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SIGNIFICANCE OF BACTEREMIA CAUSED BY STAPHYLOCOCCUS AUREUS

A STUDY OF ONE HUNDRED AND TWENTY-TWO CASES AND A REVIEW OF THE LITERATURE CONCERNED WITH EXPERIMENTAL INFECTION IN ANIMALS

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Within recent years there has been an increasing interest in the various aspects of infections caused in both man and animals by Staphylococcus aureus. In order to gather more information concerning the factors that influence the course of these infections in man, we have studied a group of 122 cases of bacteremia in which the causative agent was Staph. aureus. We were especially interested in analyzing these cases in the light of experimental infections as they have been produced in animals by numerous investigators.

ANALYSIS OF CASES

The 122 cases were observed at the Boston City Hospital over a seven year period. In all cases, the patients had demonstrable bacteremia on one or more occasions and the clinical course was entirely consistent with a severe infection. In only 22 cases did the patients recover, a fatality rate of 81.97 per cent.

Seasonal and Sex Incidence.—There was no peak of incidence at any season of the year, although there were a few more cases in the winter and in the summer than at other seasons. In 66 per cent of cases the patients were males and in 34 per cent females, with the same relative number of deaths in each sex group, 63 and 37 per cent, respectively.

Age Incidence.—Most of the patients (67.2 per cent) were under 40 years of age, with the extremes at 10 weeks and 72 years. In 57

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per cent of the cases bacteremia occurred during the second, third or fourth decade, the greatest number being in the second (27, 16 and 13 per cent, respectively). Of the 40 patients over 40 years old, only 1 recovered, whereas 77 per cent of the recoveries occurred in patients younger than 30 years (fig. 1). The influence of the age of the patient on other factors concerned with the bacteremia will be discussed presently.

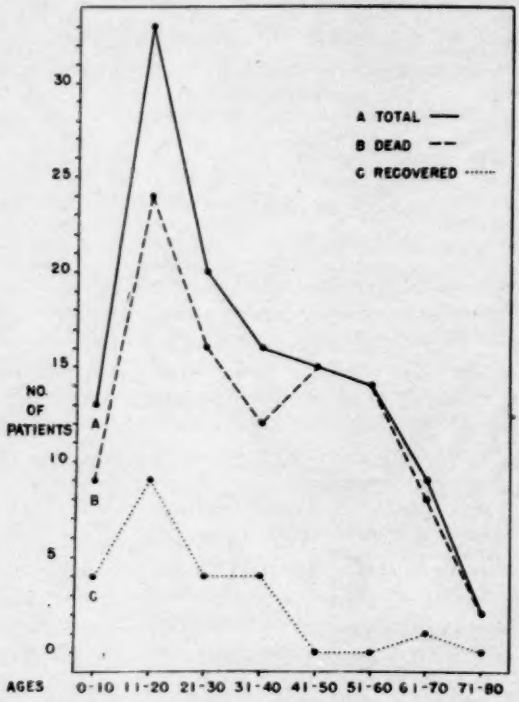

Fig. 1.—Age incidence of patients surviving and recovering in 122 cases of bacteremia caused by Staph. aureus.

Portal of Entry.—There were four common portals of entry for the agent causing bacteremia: the skin, the respiratory passages, the bones and the genitourinary tract. In 12 cases the portal of entry was undetermined (table 1).

Of the 57 cases in which the portal of entry was the skin, in 24 the infected area was located on the face, head or neck. In only 1 case of the 24 did the patient, who had a carbuncle on the neck, recover. The

location of the infection in 17 cases was the lower extremity, and in 4 the patient recovered. The types of lesions may be listed as follows:

	No. of Cases
Boils and carbuncles	30
Infected wounds	14
Infected vesicles	9
Areas of cellulitis	2
Infected areas of arteriosclerotic gangrene	2

In 17 cases it seemed clear that bacteremia followed a rupture of the local defense mechanism. In 10 of them the primary abscess was

TABLE 1.—*Portal of Entry of Organism in One Hundred and Twenty-Two Cases of Bacteremia Caused by Staphylococcus Aureus*

Portal of Entry	Number of Cases			Mortality Rate, Per Cent
	Total	Recovery	Death	
A. Skin	57	8	49	86.0
Face	12	0	12	
Head	4	0	4	
Neck	8	1	7	
Hand	3	0	3	
Arm	5	1	4	
Foot	2	0	2	
Leg	6	0	6	
Hip	2	1	1	
Thoracic wall	1	0	1	
Abdominal wall	1	1	0	
Vesicle	7	3	4	
Multiple	6	1	5	
B. Respiratory tract	30	4	26	86.7
Infections of the upper respiratory tract	20	3	17	
Pneumonia	5	0	5	
Sinusitis	2	1	1	
Peritonsillar abscess	1	0	1	
Otitis media	1	0	1	
Empyema	1	0	1	
C. Bone	11	5	6	54.5
Primary osteomyelitis	11	5	6	
D. Genitourinary tract	11	3	8	72.7
Puerperal sepsis	3	0	3	
Pyelonephritis	4	2	2	
Infection of the prostate gland	3	1	2	
Cystitis	1	0	1	
E. Circulatory system				
Phlebitis	1	1	0	00.0
F. Unknown	12	1	11	91.7

surgically incised, and in 7 the infected area was rubbed, squeezed or picked.

In 30 cases the respiratory passages were the portal of entry. Of 20 patients who had infections of the upper respiratory passages, only 3 recovered. Five patients had primary pneumonia, and they all died. None gave a history of a preceding infection of the upper respiratory tract. A peritonsillar abscess, otitis media and empyema were the source of infection in 1 case each; in all 3 cases the patient died. Of the 2 patients with sinusitis 1 recovered and 1 died.

In the 11 cases of "primary" osteomyelitis no history of a preceding staphylococcic infection was obtained, although in 5 of them there was a history of mild trauma, e. g. striking the knee a few days before the onset of the signs of infection.

Of the 11 cases in which the portal of entry was the genitourinary tract, there were 3 of puerperal sepsis. In 2 of them infection followed an abortion. In the other 8 cases the condition occurred in males. Three patients had an abscess of the prostate gland, and 1, cystitis. Three patients had acute pyelonephritis, and 1 recovered; bacteremia developed in another during the course of chronic pyelonephritis, but the patient recovered. In 2 of these patients bacteremia appeared after urethral instrumentation.

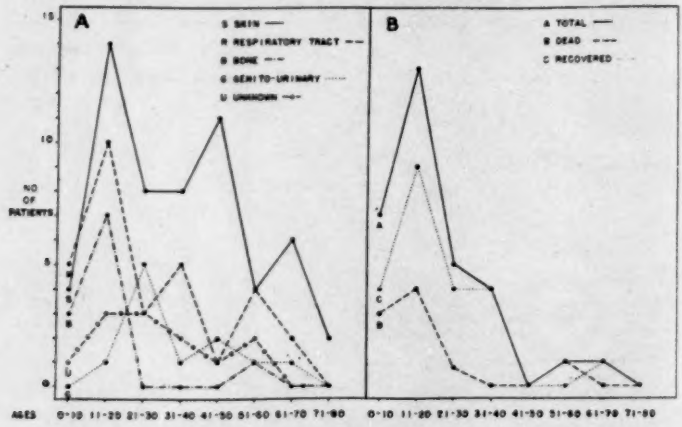

Fig. 2.—Relation of age incidence of patients to (*A*) portal of entry and (*B*) occurrence of focalized infections in 122 cases of bacteremia caused by Staph. aureus.

There was no relation between the season and the portal of entry, except in the case of the respiratory tract. Of 30 cases in which the infected area was in the respiratory tract, the infection in 10 began in the winter and in 10 it began in the spring.

However, there was some relation between the portal of entry and the age of the patient. In general, the age incidence with reference to each portal of entry parallels that of the entire series (fig. 2*A*). The most striking correlation between the portal of entry and the age of the patient occurred among those for whom the portal was the skin, the respiratory tract or bone; the greatest incidence was in the second decade. In the group of patients with infections of skin there was a secondary peak of incidence in the fifth decade and in the group with

osteomyelitis, in the sixth, whereas in the group with infections of the respiratory tract the incidence declined with increasing age, except for a slight rise in the sixth decade. The 3 patients with puerperal sepsis were in the third decade of life. The other patients in whom the portal of entry was the genitourinary tract were all in the decades from the second to the seventh, inclusive; there was no peak of incidence in any one decade. The 1 patient with phlebitis was in the seventh decade, and the patients for whom a portal of entry could not be determined were evenly distributed throughout the first six decades.

Course and Clinical Features.—The average duration of the infection was thirty-three days, the shortest being two days and the longest three hundred and twenty-eight days. Of 47 patients whose illness lasted ten days or less, all died. Of the 29 patients surviving longer than thirty-three days, 18 recovered. The illness of most of the patients who recovered took a prolonged course after the infection was focalized in areas amenable to surgical drainage. There was no direct relation between age and the duration of the disease, although the course was more protracted in the younger patients who recovered.

Thirty patients had chills, and the majority (82 per cent) of patients had remittent fever (with temperatures constantly higher than 101.1 F.); some (14 per cent) had intermittent fever (with temperatures which were normal or subnormal to higher than 101.1 F. daily), and a few (4 per cent) had continuous low grade fever (with temperatures always less than 101.1 F.). A larger number of patients with high remittent fever died than did those with other types of fever.

Metastatic Infections.—Secondary infection occurred in 100 cases (82 per cent), while in 22 (18 per cent) there was none. In 12 cases (9.8 per cent) there was a direct extension of the primary focus, the most common being thrombosis of the sinuses of the intracranial vault.

Of the metastatic infections, pneumonia and superficial abscess were the most common. Less common were internal abscess, which could be diagnosed clinically, and osteomyelitis. In 36 patients multiple metastatic infections appeared. These various types of secondary infection are summarized in table 3.

There was no correlation between the portal of entry and the appearance of secondary infection. It was noted, however, that a metastatic abscess developed more commonly in patients with superficial abscess of the skin than in those with "primary" osteomyelitis. It was also found that a superficial abscess followed an infection of the respiratory tract as frequently as did pneumonia (table 2). The relation of age to the occurrence of metastatic infection is recorded in figure 2 *B*.

Local Abscesses Treated Surgically.—In 31 patients the infection was focalized after the onset of bacteremia, so that an abscess developed

TABLE 2.—*Relation of Secondary Infection to Portal of Entry*

Secondary Infection	Portal of Entry						Number of Cases and Outcome			
				Genitourinary Tract						
	Skin	Respiratory Tract	Bone	Puerperal Sepsis	Other Types of Infection	Unknown	Total	Recovery	Death	Mortality Rate, Per Cent
None	8	5	4	1	2	2	22	2	20	90.9
Direct extension	8	2	0	1	1	0	12	0	12	100.0
Sinus thrombosis	6	1	0	0	0	0	7	0	7	
Meningitis	2	1	0	0	0	0	3	0	3	
Peritonitis	0	0	0	1	1	0	2	0	2	
Metastatic infection										
Pneumonia	20	10	2	1	1	3	37	0	37	100.0
Meningitis	2	1	0	0	0	4	7	0	7	100.0
Erysipelas	2	4	0	0	0	0	6	1	5	83.3
Acute endocarditis	1	0	0	1	0	5	7	0	7	100.0
Acute pericarditis	1	2	1	0	0	0	4	1	3	75.0
Empyema	1	2	0	0	0	0	3	0	3	100.0
Superficial abscess *	14	10	3	0	4	2	33	10	23	69.7
Skin	12	5	2	0	1	2	22	8	14	
Joints	2	4	0	0	2	0	8	1	7	
Muscles	0	1	1	0	1	0	3	1	2	
Internal abscess	12	5	0	0	2	2	21	5	16	76.2
Cerebral	3	1	0	0	0	1	5	0	5	
Pulmonary	3	2	0	0	0	0	5	0	5	
Epidural	2	0	0	0	1	0	3	1	2	
Pelvic	1	1	0	0	0	0	2	1	1	
Perinephritic	2	0	0	0	0	0	2	2	0	
Pyonephrotic	1	0	0	0	1	0	2	0	2	
Pretracheal	0	1	0	0	0	0	1	0	1	
Thyroiditis	0	0	0	0	0	1	1	1	0	
Osteomyelitis	9	5	0	0	0	0	14	8	6	42.9
Multiple metastases	17	11	2	1	1	4	36	5	31	86.1

* With associated phlebitis, 1 case.

which was amenable to surgical treatment (table 3). These patients had localized collections of pus in the skin, the subcutaneous tissue, the muscles, the bones or the pleural cavity. In all 22 patients who recovered the infection was focalized into superficial abscesses, with no demonstrable deep infections. All of these patients who recovered received surgical treatment, except 1. In this patient thyroiditis developed but subsided without surgical intervention. The fatality rate for these 31 patients was lower (29 per cent) than that for the entire series (81.97 per cent).

The majority (93.5 per cent) of the patients in whom foci of infection developed were under 40 years of age; only 2 were over 40, and 1 of them recovered. The age incidence of these patients parallels that of the entire series.

TABLE 3.—*Incidence of Localized Infection Following Bacteremia Originating at Various Portals of Entry*

Portal of Entry	Incidence			
	Complete Series		Localized Infection	
	Number of Cases	Percentage of Cases	Number of Cases	Percentage of Cases
Skin	57	46.7	12	38.7
Respiratory tract	30	24.6	7	22.6
Bone	11	9.0	7	22.6
Genitourinary tract				
Puerperal sepsis	3	2.5	0	00.0
Other types of infection	8	6.6	3	9.7
Circulatory system (phlebitis)	1	0.8	1	3.2
Unknown	12	9.8	1	3.2
Total	122		31	

The portals of entry for these 31 patients were also of the same relative frequency as were those for the entire series, except that here there was a slightly smaller number of persons with infected areas of skin as the portal and a moderately greater number with osteomyelitis as the source of bacteremia.

The course of the disease among these patients was similar to that of the series as a whole, except that the duration was longer. With 1 exception all those patients whose infection could be focalized and who survived for thirty days recovered, although many had a protracted illness. This 1 patient died in a secondary wave of bacteremia, which apparently arose from the chronic osteomyelitis resulting from the primary wave.

Factors Influencing Bacteremia.—Several factors influenced the occurrence and the course of the bacteremia. For purposes of discussion they can be divided into two groups, dealing with (1) the nature

and management of the primary focus, and (2) the presence of debilitating diseases, such as diabetes, arteriosclerosis, heart disease and cancer (table 4).

One of the factors concerned with the pathogenesis of bacteremia was the rupture of the local defense mechanism by the incision of an abscess. There were 21 cases of such a rupture, and in only 2 did the patient recover. In most cases the infection was localized in the skin in the form of a furuncle or a carbuncle, which usually had been incised shortly before the development of bacteremia. In 1 case a peritonsillar abscess had been opened; in 1 empyema had been drained; in 1 a toe nail had been removed from a gangrenous toe, and in 7 a small furuncle had

TABLE 4.—*Factors Influencing Portal of Entry and the Outcome of Bacteremia*

Factors	Portal of Entry						Number of Cases and Outcome		
				Genitourinary Tract					
	Skin	Respiratory Tract	Bone	Puerperal Sepsis	Other Types of Infection	Unknown	Total	Recovery	Death
Rupture of local defense mechanism	19	2	0	0	0	0	21	2	19
Wound	13	0	0	0	2	0	15	0	15
Trauma	11	0	5	2	0	1	19	8	11
Diabetes mellitus	6	1	0	1	0	1	9	0	9
Arteriosclerosis	6	3	0	0	0	0	9	0	9
Heart disease	7	8	0	1	0	2	18	1	17
Arteriosclerotic	4	3	0	0	0	0	7	0	7
Rheumatic	1	4	0	0	0	2	7	0	7
Hypertensive	2	1	0	1	0	0	4	1	3
Cancer	0	1	0	0	0	0	1	0	1

been squeezed. Two of these patients had diabetes, and 1 had arteriosclerosis. Bacteremia following the rupture of the local defense mechanism occurred at all ages, an age incidence paralleling that of the entire series. In 7 of the patients pneumonia developed, and in 6 the infection spread by direct extension from the primary focus to the surrounding tissues (table 5.). The experience with these patients would serve to emphasize the dangers of rupturing the local defense mechanism of the body once an abscess has formed and the necessity of great care in draining such an abscess without injury to the surrounding tissues.

There were 15 cases of infection of a wound, with associated bacteremia, and in all cases the patient died. In 7 cases the wound was traumatic in origin; in 2 it was a trophic ulcer, in 2 the result of an abortion and in 1 the result of another type of operation. Of the other 8 cases, the infection in 1 followed a bite by a mouse, in 1 an insect bite and in 1 a liberal covering of a herpes simplex with lipstick. In 2

of these cases there were no metastases; in 2 there was a direct extension of the primary infection, and in 5 pneumonia and metastatic abscesses developed.

The development of bacteremia following traumatic injury without interruption of the continuity of the skin was observed in 19 cases, with 11 deaths. The injury was often mild, and the precise relation of trauma to infection was difficult to ascertain. In 7 cases vesicles of the skin became infected, and in 2 of them the blebs were incised before the appearance of the bacteremia. Cellulitis appeared in 1 case after an application of liniment to the thoracic wall, in another after an application of petrolatum to a bruised nose and in a third case after

TABLE 5.—*Conditions Preceding and Metastatic Infections Following Bacteremia*

	Metastases							
Preceding Conditions	None	Direct Extension	Pneumonia	Pneumonia with Associated Conditions *	Superficial Abscess	Internal Abscess	Osteomyelitis	Multiple Abscesses
Rupture of local defense mechanism	3	6	7	a	4	1	3	6
Wound	2	2	5	0	3	2	1	2
Trauma	6	0	3	b	6	1	5	4
Diabetes mellitus	4	0	1	a	4	1	0	2
Arteriosclerosis	3	0	4	a	2	1	0	2
Heart disease								
Arteriosclerotic	2	0	4	a	1	0	0	1
Rheumatic	1	0	2	c, d, e	0	1	1	2
Hypertensive	1	0	1	a	1	0	0	1
Cancer	1	0	0	0	0	0	0	0

* The following symbols have been used: a, erysipelas, 1 case; b, empyema, 1 case; c, meningitis, 1 case; d, acute pericarditis, 1 case, and e, acute endocarditis, 3 cases.

an accident which injured the leg. Of the cases of infections of the genitourinary tract bacteremia appeared in 2 after repeated passage of sounds or catheters; in another case cystitis, and later bacteremia, appeared after a fall which caused multiple fractures of one leg. Five patients had "primary" osteomyelitis and gave a history of mild trauma to the involved bone a few days before the onset of bacteremia but denied having a preceding infection. A mild blow to an old focus of infection in the thumb appeared to have reactivated the infection and given rise to bacteremia in 1 case. In 6 of these cases there were no metastases; in 6 there were metastatic superficial abscesses, and in 5 secondary osteomyelitis developed.

The presence of debilitating diseases was of significance in both the development and the outcome of the bacteremia. There were 9 patients with diabetes mellitus and bacteremia, and all of them died. The portal of entry was an area of infection of the face or neck in 4 cases,

an infected foot in 1 case, an infected prostate gland in 1, the skin (multiple boils) in 1 and an undetermined source in 1. Two of the patients who had an abscess of the face had the abscess opened before the onset of the bacteremia. In 1 the infected area was surgically incised, and in the other it was traumatized by squeezing. Four patients had arteriosclerosis, and 2 of them also had heart disease. Six of the diabetic patients were women and 3 were men; all were over 30 years of age, 56 per cent being over 50.

High grade arteriosclerosis was a predisposing factor in 9 cases. In 6 the portal of entry was an area of superficial infection of the skin; in the other 3, the respiratory tract. One patient had the nail removed from a grangrenous toe before the onset of bacteremia, and in another bacteremia followed a hatchet wound. Four patients also had diabetes, and 7 had arteriosclerotic heart disease as well. All the patients were in the seventh or the eighth decade of life, except 1 aged 49, who had a coronary occlusion during the course of bacteremia.

Heart disease was present in 16 patients, who could be divided into three groups: those with rheumatic, those with arteriosclerotic and those with hypertensive heart disease. The second group, in which there were 7 patients, includes some of those discussed in the preceding paragraph. There were 7 patients with rheumatic heart disease. By age they were evenly distributed throughout the second, third and fourth decades of life. The portal of entry was an area of superficial infection of the skin in 1, an unknown portal in 2, and an area of infection in the upper respiratory tract in the other 4. In the first patient acute bacterial endocarditis developed, with meningitis and osteomyelitis. Of the next 2 patients, acute bacterial endocarditis developed in 1 and subacute bacterial endocarditis in the other. Two of the others died of acute bronchopneumonia, and 2 had fulminating septicemia, with questionable acute pericarditis in 1 instance. There were 4 patients with hypertensive heart disease, 2 of whom also had arteriosclerotic heart disease. One of the other 2 died of sepsis and shock after a traumatic amputation of a leg. The fourth patient, aged 49, had hypertensive heart disease secondary to pyelonephritis and renal insufficiency. A large abscess formed; a culture of the blood was found to be positive for Staph. aureus, and the abscess healed.

One patient had a bronchiogenic carcinoma with (secondary) chronic empyema. Suddenly bacteremia developed, and he died.

TREATMENT

The treatment in these 122 cases varied from year to year. General supportive measures, blood tranfusions, surgical drainage of foci of infection, administration of antitoxin and chemotherapy were used in different cases (table 6). Of the 75 patients receiving only general

treatment, 63 died, a fatality rate of 84 per cent. Thirty-two had supportive treatment alone, and 9 also received blood transfusions; all 41 died. Two of the 16 patients having supportive and surgical treatment alone recovered, while 8 of 15 patients receiving supportive treatment, surgical treatment and blood transfusions recovered. The fatality rates in these two groups were 87.5 and 46.7 per cent, respectively. Four patients received antitoxin, but they all died. Of the 34 patients receiving sulfanilamide and the 8 receiving sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) 9 recovered, a fatality rate of 78.6 per cent.

Every one is in agreement that the fatality rate in patients with staphylococcic bacteremia is high, and, regardless of the treatment which has been recommended, the fatality rate has been recorded as between 53 and 91 per cent by several groups of physicians.

TABLE 6.—*Treatment in One Hundred and Twenty-Two Cases of Bacteremia Caused by Staphylococcus Aureus*

Treatment	Number of Cases and Outcome			
	Total	Recovery	Death	Mortality Rate, Percentage
General	75	12	63	84.0
Supportive	32	0	32	
Supportive and transfusion	9	0	9	
Supportive and surgical	16	2	14	
Supportive, transfusion and surgical	15	8	7	
General and nonspecific agents	3	2	1	
General and antitoxin	4	0	4	100.0
General and sulfanilamide	34	9	25	73.5
General and sulfapyridine	8	0	8	100.0

From the experiences that have been reported with reference to infection in animals and from the recorded experience with reference to infection in man, it would appear that the following methods of treatment should be recommended: (1) administration of antitoxin for the neutralization of circulating toxin; (2) blood transfusions to supply red cells and leukocytes; (3) surgical drainage of all foci of infection, and (4) the use of large amounts of sulfapyridine or sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole).

COMMENT ON CLINICAL CASES

In summing up, then, one is justified in saying that bacteremia caused by Staph. aureus is of grave significance since it is followed by a high fatality rate. The common sources for invasion of the blood are the skin, the respiratory tract, the bones and the genitourinary tract. In a few cases it is not possible to determine the portal of entry. Bacteremia is frequently preceded by a rupture of the local defense mechanism by such measures as traumatizing a focus of infection, and

it is more frequent and serious in elderly patients with arteriosclerosis, diabetes or heart disease.

On the basis of the clinical course of illness the cases could be divided into four groups: those showing (1) bacteremia with no metastatic infection and rapid death, 20; (2) bacteremia with metastatic abscess and death, 70; (3) clearance of bacteremia with metastatic abscess and death, 10, and (4) clearance of bacteremia with drainage of metastatic abscess and recovery, 22.

Metastatic lesions were common and occurred in 82 per cent of the cases. When metastatic lesions failed to appear, the course of the disease was usually rapid and death occurred within two to ten days after the appearance of the first symptoms. In 2 cases of "primary" osteomyelitis no metastases were discernible, the infection being localized to the primary site and the patient recovering. Undoubtedly in such cases the "primary" osteomyelitis is an infection which is secondary to that at some undetected portal of entry. The commonest metastatic lesions were found in the skin, in the subcutaneous tissues and in the lungs. Although abscesses in other tissues were not infrequent, inasmuch as we selected for study a group of patients who had demonstrable bacteremia, the numerous cases of staphylococcic abscess in such organs as the kidney and the perirenal tissues and in other organs in which bacteremia was not demonstrable were not included. If one had an opportunity of following all cases of such abscess from the beginning of the infection, it might be possible, in many at least, to detect bacteremia early in the course of the disease and before the development of an abscess. Those cases would then fall into groups 3 and 4 as just described.

When recovery takes place, the blood stream is cleared of organisms and either the focus of infection which is responsible for the bacteremia is drained or a metastatic abscess is focalized and drained. This is observed more often in patients under 40 years of age than it is in older ones.

In the group of patients who recovered, the illness ran a protracted course on account of metastatic infection. In the group of patients who died the duration of illness was usually less than thirty days, and the largest number died in the first ten days.

Up to the present time, the treatment of staphylococcic bacteremia is unsatisfactory. The use of blood transfusions, with surgical drainage of purulent foci of infection, was the only form of therapy that seemed to be at all helpful, but even with this treatment the fatality rate remained over 50 per cent (53.3 per cent). It is interesting that there are no significant differences between the fatality rate for the whole series (81.97 per cent), that for the portion in which sulfanilamide or sulfapyridine (78.6 per cent) was given and that for the remainder (83.8 per cent).

REVIEW OF THE LITERATURE CONCERNING ANTIGENIC STRUCTURE AND ANIMAL EXPERIMENTATION

In view of the foregoing observations, it was of interest to review the important experimental work dealing with infections caused by Staph. aureus. The antigenic structure of the staphylococcus, so far as it is known, is summarized in table 7.

The cultural characteristics of the staphylcococus were studied forty to fifty years ago and are too well known to need further description. More recently an attempt has been made to correlate the biologic characteristics of the organism with its virulence. It has been found that its pathogenicity is more accurately determined by its antigenic power than by its cultural characteristics.[1] One of the best single cultural tests of virulence is that of mannitol fermentation, which Julianelle [2] claimed is accurate for at least 95 per cent of all strains. Chapman and his co-workers [3] stated that the pathogenicity of a given organism can be determined with a high degree of accuracy by correlation of three of its properties, color, coagulase production and hemolytic activity, and that the best of these for a single test is coagulase production.

The problem of staphylococcic dissociation and the relation of this phenomenon to virulence has just been attacked, and as yet the conclusions are not clearly defined. By means of type-specific precipitins Julianelle and associates separated staphylococci into two types, A and B, of which type A is pathogenic.[4] Thompson and Khorazo [5] divided the nonpathogens into at least two groups. Hoffstadt and

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3. (*a*) Chapman, G. H.; Berens, C.; Peters, A., and Curcio, L.: Coagulase and Hemolysin Tests as Measures of Pathogenicity of Staphylococci, J. Bact. **28**:343-363, 1934. (*b*) Chapman, G. H.; Berens, C.; Nilson, E. L., and Curcio, L. G.: The Differentiation of Pathogenic Staphylococci from Non-Pathogenic Types, ibid. **35**:311-334, 1938.

4. (*a*) Julianelle, L. A., and Wieghard, C. W.: The Immunological Specificity of Staphylococci: I. Occurrence of Serologic Types, J. Exper. Med. **62**:11-22, 1935. (*b*) Wieghard, C. W., and Julianelle, L. A.: The Immunological Specificity of Staphylococci: II. The Chemical Nature of the Soluble Specific Substances, ibid. **62**:23-30, 1935. (*c*) Julianelle, L. A., and Wieghard, C. W.: The Immunological Specificity of Staphylococci: III. Interrelationships of Cell Constituents, ibid. **62**:31-37, 1935. (*d*) Julianelle, L. A., and Hartmann, A. F.: The Immunological Specificity of Staphylococci: IV. The Cutaneous Reactions to the Type-Specific Carbohydrate, ibid. **64**:149-159, 1936.

5. (*a*) Thompson, R., and Khorazo, D.: Antigenic and Biochemical Properties of Staphylococci, J. Bact. **33**:51-52, 1937; (*b*) Correlated Antigenic and Biochemical Properties of Staphylococci, ibid. **34**:69-79, 1937.

TABLE 7.—*Summary of Data Concerning the Antigenic Structure of the Staphylococcus*

Constituents	Structure	Antigenicity	Thermal Resistance	Biologic Properties	Author
Organism					
Whole	.....	+	.....	Pathogenicity; pigment production; agglutinability	Kolle and Otto (Ztschr. f. Hyg. u. Infektionskr. **41**: 369-379, 1902)
P	Protein	+	.....	Common to gram-positive cocci	Lancefield (J. Exper. Med. **42**: 397-412, 1925). Julianelle and Wieghard.[4a] Wieghard and Julianelle.[4b] Julianelle and Wieghard [4c]
C	Carbohydrate	0	Stable	Type-specific; haptene; types A, B and C	Julianelle and Wieghard.[4a] Wieghard and Julianelle.[4b] Julianelle and Wieghard.[4c] Thompson and Khorazo [5]
Capsule	.....	+ (in antibacterial antibodies)	Stable	Found in 3 hr. broth cultures of toxigenic strains; not formed during growth in serum; grows within leukocytes; destroyed by shaking; resists phagocytosis	Lyons [26]
				Existence questioned	Spink [27]
Toxin					
α hemolysin	.....	+	Labile	Hemolyzes human, sheep and rabbit red cells; dermonecrotic and intravenous lethal properties (possibly identical)	Kraus and Clairmont (Wien. klin. Wchnschr. **13**: 49-56, 1900). Julianelle and Wieghard [18]
α hemolysin	.....	+	? Stable	Hemolyzes rabbit red cells; dermonecrotic for guinea pigs	Dolman and Kitching (J. Path. & Bact. **41**: 137-162, 1935)
α_2 hemolysin	.....	+	? Stable	Hemolyzes rabbit red cells; end point of titration displaced	Morgan and Graydon [8]
β hemolysin	.....	+	Labile	Found especially in bovine strains; hot-cold lysin for sheep red cells; nonlethal; causes flush on intradermal injection	Bigger, Boland and O'Meara (J. Path. & Bact. **30**: 271-277, 1927). Glenny and Stevens (ibid. **40**: 201-210, 1935)
α β hemolysin	.....	?	?	Found in human and bovine strains; causes α hemolysis of rabbit red cells, β hemolysis of sheep red cells	Bryce and Rountree [19]
γ hemolysin	.....	+	Labile	Hemolyzes sheep and rabbit red cells; differs from α and β hemolysins; may be identical with α_2 hemolysin	Flaum and Forssman.[9] Smith.[10] Smith and Price [11]
Dermatonecrotic	.....	+	Labile	Intradermal injection causes necrosis (rabbit and guinea pig)	Parker (J. Exper. Med. **40**: 761-772, 1924), Burnet [13]
Intravenous lethal	.....	+	Labile	Intravenous injection causes sudden death (mouse, guinea pig, rabbit)	Burnet.[13] Kraus and Pribram (Wein. klin. Wchnschr. **19**: 493-494, 1906)
Leukocidin (Neisser and Wechsberg)	.....	+	Labile	Destroys rabbit leukocytes; probably identical with hemolysin [12]	Van de Velde (Cellule **10**: 401-460, 1894). Neisser and Wechsberg (Ztschr. f. Hyg. u. Infectionskr. **36**: 299-349, 1901)
Leukocidin (Panton and Valentine)	.....	+	?	Destroys human leukocytes.....	Panton and Valentine [12]
Gastrointestinal	.....	+	Labile	Oral ingestion produces symptoms of acute food poisoning	Dack, Carey, Woolpert and Wiggers (J. Prev. Med. **4**: 167-175, 1930). Jordan, Dack and Woolpert (ibid. **5**: 383-386, 1931). Jordan [24d]
Coagulase	? Enzyme	0	Stable	Coagulates plasma (human, horse, ox, sheep, guinea pig, etc.)	Loeb (J. M. Research **10**: 407-419, 1903). Much (Biochem. Ztschr. **41**: 143-155, 1908). Cruickshank [26b]
Fibrinolysin	? Enzyme	0	Stable	Destroys fibrinogen and fibrin in hours or days (slowly destroys clot)	Much. Fisher (Bull. Johns Hopkins Hosp. **39**: 419-422, 1926)

Youmans [6] and Chapman and associates,[2b] among others, have shown that dissociants of decreasing virulence can be produced from a virulent strain of staphylococcus. Hoffstadt and Youmans stated that, as shown in their earlier work, these dissociants have a lighter color and less hemolytic and coagulating power. Attempts by Hoffstadt and Clark [7] to analyze chemically the structure of virulent and of avirulent staphylococci are as yet inconclusive.

The staphylococcic toxin which has received the most attention and against which antiserums are tested is the hemolysin. This toxin hemolyzes rabbit, sheep and human red cells, the rabbit cells being the most sensitive and the human the least sensitive. The experimental results are confused by the use of different strains of organisms and different species of cells. For instance, the bovine strains of staphylococci produce the most β hemolysin, while human strains produce the most α hemolysin. The entire action of Morgan and Graydon's α_1 and α_2 hemolysins [8] has not yet been determined. Flaum and Forssman [9] have described another hemolysin which differs from both α and β lysin.[10] Smith and Price [11] termed this the γ hemolysin and stated that it may be identical with the α_2 hemolysin. Panton and Valentine [12] claimed that hemolysin for human red cells probably differs from that which is active against rabbit cells. It would appear, then, that one of the toxic substances elaborated by the staphylococcus hemolyzes erythrocytes and is antigenic and that its action varies with the strain employed and the species of red cells that are used in the test.

The dermatonecrotic and intravenous lethal toxins require no special comment, except that the precise mechanism for the action of the lethal toxin is not known.[13] Kellaway and associates,[14] studying the

6. Hoffstadt, R. E., and Youmans, G. P.: Staphylococcus Aureus, Dissociation and Its Relation to Infection and Immunity, J. Infect. Dis. **51**:216-242, 1932.

7. Hoffstadt, R. E., and Clark, W. M.: The Chemical Composition and Antigenic Properties of Fractions of the Smooth and Rough Strains of Staphylococcus Aureus, J. Infect. Dis. **62**:70-82, 1938.

8. Morgan, F. G., and Graydon, J. J.: Toxins of the Staphylococcus, with Special Reference to Estimation of Potency, J. Path. & Bact. **43**:385-401, 1936.

9. Flaum, A., and Forssman, J.: Studies on Staphylococci: V. Experimental Investigations of Staphylolysin, Acta path. et microbiol. Scandinav. **13**:263-272, 1936.

10. Smith, M. L.: Circulating Antitoxin and Resistance to Experimental Infection with Staphylococci, J. Path. & Bact. **45**:305-310, 1937.

11. Smith, M. L., and Price, S. A.: Staphylococcus γ Hemolysin, J. Path. & Bact. **47**:379-393, 1938.

12. Panton, P. N., and Valentine, F. C. O.: Staphylococcal Toxin, Lancet **1**:506-508, 1932.

13. Burnet, F. M.: The Exotoxins of Staphylococcus Pyogenes Aureus, J. Path. & Bact. **32**:717-734, 1929.

14. Kellaway, C. H.; MacCallum, P., and Tebbutt, A. H.: The Fatalities at Bundaberg, Report of the Royal Commission, M. J. Australia **2**:2-30 and 38-64, 1928.

Bundaberg disaster, noted that the toxin was noxious to heart muscle and caused circulatory collapse. From later pharmacologic studies Kellaway and other co-workers [15] concluded that the lethal toxin causes circulatory obstruction in the lungs and acts directly on the heart by constricting the coronary vessels, with resultant diminution of the coronary flow. However, he stressed the artificial conditions established by the necessary laboratory procedures.

The possibility that there is a single toxin with hemolytic, dermatonecrotic and lethal manifestations rather than three separate and distinct toxins is still being debated. Considerable suggestive, but no conclusive, experimental evidence has been presented to prove or disprove the unitarian viewpoint. Burnet,[15] Bryce and Rountree [16] and Levine,[17] among others, found that results of quantitative studies of the different toxins were strictly parallel for each strain studied, while still others for example, Burky [18] and Forssman,[19] noted quantitative and qualitative differences among the toxins.

The results of the experimental studies of staphylococcic leukocidin have been confusing and inconsistent. This is due, in large part, to the use of leukocytes from different animals.[12] Valentine [20] expressed the belief that the leukocidal action against rabbit leukocytes is probably due to the hemolysin. This view was shared by Wright.[21] On the other hand, both Valentine and Wright expressed the opinion that the leukocidin against human cells is distinct from hemolysin. They based their conclusions on the difference in the mode of destruction of the leukocytes as observed under the microscope. Proom [22] has also noted

15. Kellaway, C. H.; Burnet, F. M., and Williams, F. E.: The Pharmacological Action of the Exotoxin of Staphylococcus Aureus, J. Path. & Bact. **33**: 889-912, 1930.

16. Bryce, L. M., and Rountree, P. M.: Production of β-Toxin of Staphylococci, J. Path. & Bact. **43**:173-189, 1936.

17. Levine, B. S.: The Unity of the Hemolytic, Dermonecrotic, and Lethal Properties of Staphylococcal Exotoxin and of Their Corresponding Counterparts in Staphylococcal Antitoxin, J. Path. & Bact. **48**:291-298, 1939.

18. Burky, E. L.: Studies on Cultures and Broth Filtrates of Staphylococci, J. Immunol. **24**:93-114, 1933.

19. Forssman, J.: Studies on Staphylococci: VII. On Active Immunity Against Staphylococcal Infections and Its Relation to Known Antibodies Against Staphylococci or Products of These Bacteria, Acta path. et microbiol. Scandinav. **13**:459-485, 1936.

20. Valentine, F. C. O.: Further Observations of the Role of the Toxin in Staphylococcal Infection, Lancet **1**:526-531, 1936.

21. Wright, J.: Staphylococcal Leucocidin (Neisser-Wechsberg Type) and Antileucocidin, Lancet **1**:1002-1004, 1936.

22. Proom, H.: The Interrelationships of Staphylococcal Leucocidins, J. Path. & Bact. **44**:425-429, 1937.

this difference in the action of leukocidin on human and on rabbit cells. There is evidence that leukocidin is antigenic, and it is not difficult to believe that antileukocidal substances play a great part in the control of staphylococcic infections.

The gastrointestinal toxin is the toxin concerned in outbreaks of staphylococcic food poisoning. It is produced only by certain strains, which, however, cannot be differentiated by cultural or by biochemical tests from those strains which do not produce enterotoxin.[23] The earlier investigations, based on experiments with human volunteers, rabbits and Macaca rhesus monkeys, have been expanded recently by means of Dolman's method of intra-abdominal injection of the toxin into kittens, and results show that this toxin has definite and specific antigenic properties and differs from α and β toxins.[24]

Coagulase and fibrinolysin are not true exotoxins and probably are enzymic; probably coagulase acts like thrombin and fibrinolysin destroys fibrin and fibrinogen.[25]

Of the aforementioned bacterial constituents and toxins, probably all except the β hemolysin [20] are concerned in human infections, the α_1 and α_2 hemolysins being considered as α hemolysin. The enterotoxin probably is involved only in infections with certain strains, as is the fibrinolysin which also acts so slowly as to be of questionable effect.[25b] The analogy has often been drawn between the dermonecrotic effect in experimental infections and the progress of events in surface infections in human beings. As yet the role of the lethal toxin in infections in man has not been worked out.

The role of hemolysin in infections in human beings is not fully understood. In certain cases of severe infection marked anemia and jaundice develop, a fact which could be explained on the basis of the action of hemolysin. Panton and Valentine [12] studied a group of strains from different sources and titrated the production of hemolysin and of

23. Kupchik, G. J.: Some Cultural and Biochemical Characteristics of Enterotoxic Staphylococci, J. Infect. Dis. **61**:320-324, 1937.

24. (*a*) Dack, G. M.; Jordan, E. O., and Woolpert, O.: Attempts to Immunize Human Volunteers with Staphylococcus Filtrates That Are Toxic to Man When Swallowed, J. Prev. Med. **5**:151-159, 1931. (*b*) Woolpert, O. C., and Dack, G. M.: The Relation of the Gastro-Intestinal Poison to Other Toxic Substances Produced by Staphylococci, J. Infect. Dis. **52**:6-19, 1933. (*c*) Dolman, C. E., and Wilson, R. J.: Experiments with Staphylococcal Enterotoxin, J. Immunol. **35**: 13-30, 1938. (*d*) Jordan, E. O.: The Production by Staphylococci of a Substance Causing Food Poisoning, J. A. M. A. **94**:1648-1650 (May 24) 1930.

25. (*a*) Fisher, A. M.: The Plasma Coagulating Properties of Staphylococci, Bull. Johns Hopkins Hosp. **59**:393-414, 1936. (*b*) Cruickshank, R.: Staphylocoagulase, J. Path. & Bact. **45**:295-303, 1937.

leukocidin. The results fell into four groups, the four possible combinations being:

1. Leukocidin high, hemolysin low
2. Leukocidin high, hemolysin high
3. Leukocidin low, hemolysin high
4. Leukocidin low, hemolysin low

Strains falling in group 1 were found to be commonly associated with severe (pyemic) infections, whereas those in group 3 were associated with the superficial, sycotic type of infection of the skin. Later Valentine [20] showed that patients with corresponding infections had antiserum titers in the proportions which would be expected from a study of the different strains. These observations are of interest in the light of the recent studies of Lyons.[26] He expressed the belief that the capsules of young organisms are not formed during growth in serum and that the organisms are phagocytosed by a nonspecific opsonin. Within the leukocyte they produce a capsule and secrete their toxins; by destroying the cell they are again liberated into the blood stream.[27]

Forssman,[28] on the basis of clearance experiments, stated that when suspensions of staphylococci are injected intravenously into normal rabbits the organisms are rapidly phagocytosed by the reticuloendothelial cells. This was most noticeable in the liver, spleen and bone marrow, which contain the greatest number of such cells. Colony counts of such organs are high immediately after injection and drop rapidly. Contrasted with this are the colony counts from heart and muscle, which are low at first and increase with elapsed time, despite the appearance of leukocytes in such areas. In normal animals the colony counts of blood show a steady increase after a slight initial drop.

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26. Lyons, C.: Antibacterial Immunity to Staphylococcus Pyogenes, Brit. J. Exper. Path. **18**:411-422, 1937.

27. In recent studies Spink (Attempts to Demonstrate a Surface Antigen of Staphylococci and Specific Phagocytosis, Proc. Soc. Exper. Biol. & Med. **40**:549-552, 1939) has failed to demonstrate capsules in the staphylococcus and has found the bactericidal power of the blood of patients with chronic staphylococcic infection to be of low titer or to be entirely absent. That is to say, a patient may have an active localized infection without any bactericidal antibodies demonstrable in the circulating blood by the whole blood technic. The interpretation of these observations will require further studies, since it is not unlikely that the leukocytes are destroyed and hence the presence of antibodies may not be demonstrable by this method.

28. Forssman, J.: (*a*) Studies on Staphylococci: IX: On the Mechanism in Staphylococcal Infection and Immunity, Acta path. et microbiol. Scandinav. **14**: 468-477, 1937; (*b*) Staphylokokkenstudien: X. Verbreitung der Staphylokokken in Kaninchen nach intravenösen Injektionen von Staphylokokken, Ztschr. f. Immunitätsforsch. u. exper. Therap. **91**:165-175, 1937.

In animals immunized with toxoid—principally α hemolysin—the blood is not cleared, but there is no secondary increase in the bacteremia and the survival time is prolonged.[29] Lyons [26] presents experimental evidence showing that in animals the serums from which contain specific agglutinins for encapsulated organisms the bacterial counts can be reduced further than the initial clearance. Immunization with vaccine also prolongs the survival time,[30] but vaccine, probably because of its indeterminate toxin content, is not so effective an agent as toxoid.[12] In treatment of the more superficial types of staphylococcic infections in rabbits [31] and in human beings,[12] vaccine therapy has little effect, whereas toxoid therapy has been more successful in treatment of such infections in man [32] if the toxin content of the toxoid used is that which corresponds to the type of infection under treatment.[12] Valentine and associates [33] have reported encouraging results in a small series of cases of staphylococcic septicemia in which treatment was with a toxoid or an antitoxin of high antileukocidal and moderate antihemolytic titers. More recently Julianelle,[34] using type A staphylococcic antiserum, has succeeded in sterilizing the blood stream of 11 of 13 patients with septicemia caused by Staph. aureus.

In short, experimental septicemia in animals may take one of four courses:

1. Normal animal: bacteria partially cleared by reticuloendothelial system; secondary wave of bacteremia; no localization; death.

2. Animal immunized with toxoid: bacteria partially cleared; no secondary wave; abscesses; death.

3. Animal immunized against capsular antigen: bacteria largely cleared; no secondary wave; abscesses; death or survival.

4. Animals the serums of which contain capsular agglutinins, antitoxin and antileukocidin: bacteria cleared; abscesses; survival.

GENERAL COMMENT

The clinical course of staphylococcic infections in human beings and that of the experimental infections in animals are similar in many respects.

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29. Burnet.[18] Smith.[10]

30. Cowan, S. T.: Staphylococcal Infection in Rabbits: Antibacterial and Non-Specific Immunity, J. Path. & Bact. **48**:545-555, 1939.

31. Downie, A. W.: A Comparison of the Value of Heat Killed Vaccine and Toxoid as Immunizing Agents Against Experimental Staphylococcal Infection in the Rabbit, J. Path. & Bact. **44**:573-587, 1937.

32. Whitby, L. E. H.: The Treatment of Staphylococcal Skin Lesions with Toxoid, Lancet **1**:1454-1456, 1936.

33. Panton, Valentine and Dix.[1b] Valentine.[20]

34. Julianelle, L. A.: Observations of the Specific Treatment (Type A Antiserum) of Staphylococcal Septicemia, Ann. Int. Med. **13**:308-316, 1939.

A survey both of the clinical cases of staphylococcic bacteremia reported herein and of records of experimental infections shows that several conditions are necessary for recovery. The blood stream must be cleared of bacteria and the infection focalized so that the infection can be treated by surgical drainage or be allowed to resolve spontaneously. This happens more often in a young person under 30 years of age. It must be emphasized that a certain number of patients die from the effects of infection even though their blood streams are cleared of organisms. In these patients the soluble products ("toxins") of the staphylococci are probably important. Presumably, in the patients who recover the "toxins" are neutralized, as well as the organisms destroyed. After the Bundaberg disaster Burnet [13] reemphasized the importance of the toxins produced by the staphylococci and showed experimentally that hemolytic, dermatonecrotic and lethal toxins were formed in vivo. However, immunization against these toxins does not protect animals against experimental infection. Panton, Valentine and Dix [35] demonstrated the role of leukocidin and the importance of antileukocidin in experimental infections and in infections in human beings, but even this antibody did not overcome the bacteremia in the cases which they reported. Forssman [25] has stressed the importance of the reticuloendothelial cells in the clearing of the blood. Finally, Lyons [26] has demonstrated capsules on young staphylococci and the fact that the blood stream is cleared in animals the serums of which agglutinate such capsulated organisms.

The evidence, then, while incomplete, indicates that recovery occurs in man only if the blood is cleared of organisms, the infection localized into abscesses and the "toxic" effects of the infection neutralized. The animals with experimental bacteremia recover only if the reticuloendothelial system is active and the serum is able to protect the leukocytes from leukocidin by means of antileukocidin and to aid phagocytosis and the clearing of the blood stream. In addition, the hemolytic, dermatonecrotic and lethal toxins must be neutralized by their respective antiserums.

SUMMARY AND CONCLUSIONS

The cases of 122 patients with bacteremia caused by Staph. aureus were studied, and the literature concerning the antigenic structure of the organism and experimental infections with the staphylococcus was reviewed.

Of the 122 patients, only 22 recovered, a mortality of 81.97 per cent.

35. Panton and Valentine.[12] Panton, Valentine and Dix.[1b] Valentine.[20]

There was no correlation between the season of the year or the sex of the patient and the occurrence of bacteremia.

The majority of the patients recovering were under 30 years of age.

There was no definite correlation between the portal of entry and the outcome. The most frequent portals of entry were the skin, the respiratory tract, the bones and the genitourinary tract, cases of puerperal infection included.

There was some correlation between the age of the patient and the portal of entry. When the portal was the skin, the respiratory tract or the bone the greatest incidence was in the second decade. In the cases of two portals, the skin and the bone, there were secondary peaks of incidence in the fifth and the sixth decade, respectively.

Of the patients who died, more did so in the first ten days of illness than in any other ten day period. Conversely, the illness of those recovering ran a protracted course.

The most constant clinical feature was the presence of high, remittent fever, which decreased after surgical treatment of an abscess.

Treatment was unsatisfactory. The best results were obtained by the drainage of an abscess, when possible, and by blood transfusions.

Secondary infection appeared in 82 per cent of the cases. In 9.8 per cent there was direct extension of the primary focus. In 72.2 per cent there was distant metastatic infection. The most common of these infections were superficial abscess and staphylococcic pneumonia.

In all the patients who recovered the infection was focalized into an abscess amenable to surgical treatment.

There were several factors which influenced either the onset or the course of the bacteremia: rupture of the local defense mechanism, wound, trauma, diabetes mellitus, arteriosclerosis, heart disease and cancer.

The virulent staphylococcus contains a type-specific carbohydrate, possesses a capsule and is capable of elaborating toxic substances, which are named according to their properties, such as hemolytic, dermatonecrotic and intravenous lethal factors, leukocidin and coagulase. Some strains are capable of producing a gastrointestinal toxin and fibrinolysin.

The course of the infection in man and that in experimental animals are parallel and can be classed under one of four types: (*a*) bacteremia without metastatic infection and with rapid death; (*b*) bacteremia with metastatic infection and death; (*c*) clearance of bacteremia with focalized metastatic infection and death, and (*d*) clearance of bacteremia with focalized metastatic infection and recovery.

Recovery of the host apparently depends on the presence of three conditions: (*a*) active and viable leukocytes and phagocytes; (*b*) anti-

bacterial antibodies, and (*c*) antibodies to the toxins, especially to the lethal toxin and to leukocidin.

REPORT OF CASES

Group 1.—Bacteremia; rapid death.

CASE 37.—A man aged 52 was well until five days before admission to the hospital, when he had a chill, which was followed by high fever and pain in the groin. Physical examination showed an extremely ill man with the signs

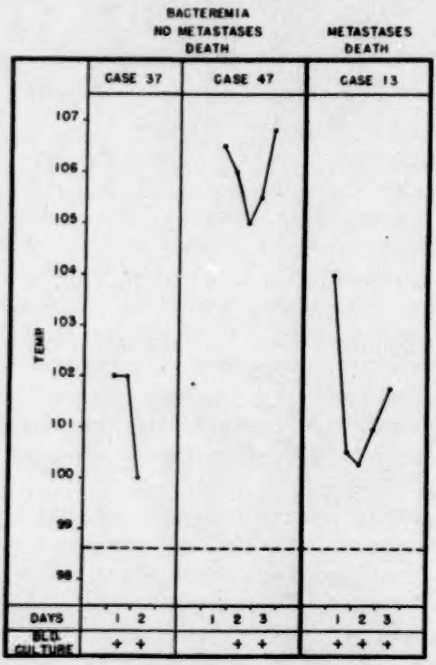


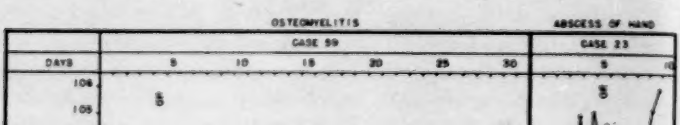
Fig. 3.—Temperature charts of 3 patients with bacteremia caused by Staph. aureus whose illness ran a fulminating course.

of bilateral bronchopneumonia. Cultures of the blood were positive for Staph. aureus on two successive days. He failed rapidly and died on the seventh day of his illness (fig. 3).

The anatomic diagnoses were: (1) staphylococcic bacteremia, (2) bilateral bronchopneumonia, (3) vegetative endocarditis of the tricuspid valve, (4) embolic nephritis and (5) jaundice.

This case was an instance of sepsis, caused by Staph. aureus and lasting only seven days, in which only bronchopneumonia was found on physical examination and the source of the bacteremia was obscure.

CASE 23.—A boy aged 8 was bitten on the left hand by a white mouse fourteen days before entering the hospital. Within several days the wound became infected, and remittent fever and the constitutional signs of infection



Necropsy showed vegetative endocarditis of the tricuspid valve, bilateral bronchopneumonia and pyelitis, with embolic nephritis. It is possible that the endocarditis was secondary to the infection of the renal tract, which was latent, and that the final episode of bacteremia was due to the vegetative endocarditis. In any event, staphylococcic endocarditis is extremely infrequently encountered at necropsy as a feature of rapidly progressing sepsis in which Staph. aureus is the causative agent. It is sufficiently common to make one consider it as a possible focus of infection in any patient who has repeatedly positive blood cultures without localizing signs. In the case of acute endocarditis the course of illness may be so rapid that the patient dies before there is destruction of the valves of the heart. In such a case cardiac murmurs are absent.

Case 47.—A boy aged 8 was well until six days before death, when he became acutely ill with high, irregular fever and pain in the groin. There were no localized signs of infection, but a culture of the blood was positive for staphylococci. Death occurred two days after admission to the hospital (fig. 3).

Necropsy showed miliary abscesses of the myocardium, spleen and pancreas, without any other lesions.

This case was an example of sepsis caused by Staph. aureus without an obvious portal of entry and without any signs of localized infection. Death occurred within six days after the onset of symptoms.

Case 13.—In a man aged 46, who had a carbuncle on the back of the neck, a chill suddenly developed, with a high, remittent fever and signs of bronchopneumonia and stupor. The course of his illness was one of progressive failure, with death occurring six days after the onset of the infection.

Necropsy showed a carbuncle of the neck and multiple abscesses of the brain, liver and kidneys.

This case was an instance of sepsis caused by Staph. aureus following an infection of the neck with multiple abscesses in various organs. The course was extremely rapid.

Group 2.—Bacteremia; multiple abscesses; death.

Case 59.—A girl aged 17 complained of pain in the right leg and fever. Examination showed fever, leukocytosis and signs of osteomyelitis of the right tibia. Culture of the blood was positive for Staph. aureus on five occasions. In spite of operative treatment for the osteomyelitis, multiple blood transfusions and administration of staphylococcic antitoxin and sulfanilamide, an abscess of the kidneys and the rectus abdominis muscles developed, and the patient died thirty-two days after the onset of the illness (fig. 4).

This case is an example of osteomyelitis with associated bacteremia and metastatic infection in the kidneys and muscles. The blood was not cleared of organisms in spite of rigorous treatment. Several abscesses were noted at necropsy.

of the abscess and the areas of osteomyelitis, the course was one of progressive failure, and the patient died twenty-three days after the onset of infection (fig. 4).

Group 3.—Bacteremia with clearing of the blood stream; metastases; recovery.

Case 44.—In a boy aged 14 the signs of acute osteomyelitis of the right tibia developed, with high, remittent fever and bacteremia. Foci of osteomyelitis subsequently developed in the humerus and metatarsal bones, and the blood stream was cleared of bacteria. The foci of osteomyelitis were drained, and the patient recovered after an illness of three hundred and twenty-eight days (fig. 5).

This case illustrates that recovery may occur in a young person with

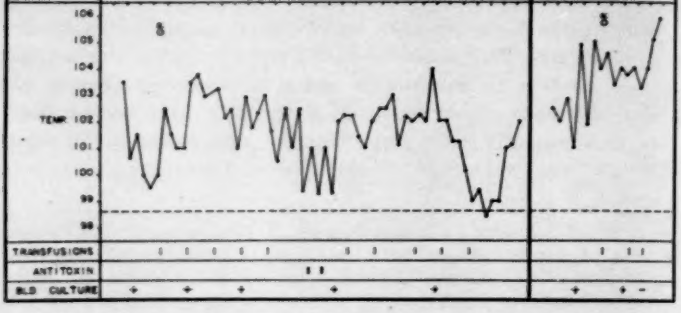


Fig. 4.—Temperature charts of 2 patients in whom bacteremia was followed by metastatic infection and death.

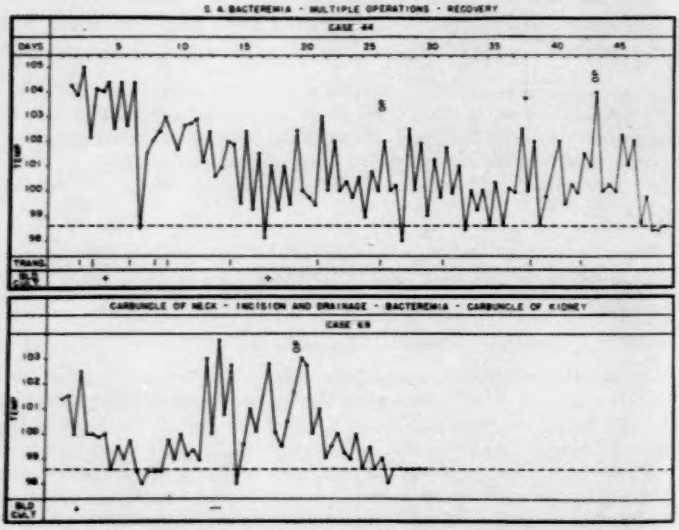


Fig. 5.—Temperature charts of 2 patients in whom bacteremia was followed by clearing of the blood stream, drainage of an abscess and recovery.

developed. At the time of admission there were signs of an infection of the subcutaneous tissues of the left hand and arm, with bacteremia and osteomyelitis of the left ulna and radius. In spite of blood transfusions and surgical drainage

METABOLISM IN ORGANIC HYPERINSULINISM

I. QUANTITATIVE STUDIES OF THE VARIATIONS IN THE RATE OF COMBUSTION OF CARBOHYDRATE PRODUCED BY ALTERATIONS IN THE DIET

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Soon after physicians had come to recognize the characteristic symptoms of insulin hypoglycemia, Harris,[1] in 1924, proposed the concept of endogenous hyperinsulinism. He had noted, in several patients, symptoms similar to those observed after an overdose of insulin and had demonstrated the presence of abnormally low levels of the blood sugar for the duration of such symptoms. He had shown, further, that the symptoms could be relieved promptly by the oral administration of carbohydrate foods. In 1927 Wilder, with others,[2] in a classic report, presented indisputable evidence that neoplastic pancreatic islet tissue, by producing excessive amounts of substance having the physiologic

was cleared of bacteria. The foci of osteomyelitis were drained, and the patient recovered after an illness of three hundred and twenty-eight days (fig. 5).

This case illustrates that recovery may occur in a young person with staphylococcic sepsis if it is possible to localize the infection in an abscess which can be drained.

CASE 69.—A woman aged 24 was admitted to the hospital, complaining of chills, fever and generalized prostration. She had been well until two weeks before entry, when a carbuncle developed on the back of the neck. This finally localized in a circumscribed area and was incised two days before her admission. Soon after the incision chills and fever developed. On admission she was acutely ill and showed a draining abscess, caused by Staph. aureus, on the back of the neck. There was irregular fever, and a blood culture made on the day of admission was positive for Staph. aureus. As the signs of inflammation disappeared from the lesion on the back of the neck, the temperature gradually became lower over a period of nine days and remained normal for two days. Then high, irregular fever began to develop once again, and, within twenty days of admission, there were distinct signs of a perinephritic abscess. This was drained through an incision in the loin. The temperature gradually fell to normal after a period of eight days. Recovery followed, and the patient left the hospital two weeks after operation.

This case was an example of a carbuncle on the neck due to Staph. aureus and followed by bacteremia after the abscess was incised. Later a metastatic lesion of the kidney and the perirenal tissues developed, and complete recovery followed only after drainage of the metastatic abscess.

ism, have been identified at operation or at autopsy, the literature contains surprisingly little quantitative information concerning the abnormal metabolism involved.

The purpose of this report is to record the results of a series of extensive metabolic studies done on a patient with severe organic hyperinsulinism both before and after the surgical removal of multiple islet cell tumors. This first group of studies compares the rate of utilization of carbohydrate in a person with organic hyperinsulinism and that in normal persons under a variety of conditions. It is known, for example, that a short period of restriction of carbohydrate in the diet of the normal person results in a significant decrease in his ability to utilize a standard dose of dextrose.[4] This is manifested by a prolonged postprandial elevation of the blood sugar, glycosuria, failure to obtain the usual rise of the respiratory quotient and increased catabolism of protein. A similar, but more severe, depression of the ability to metabolize a test dose of dextrose has been shown to occur in starving dogs. This abnormality is completely corrected in three to five days by the daily administration of 50 Gm. of dextrose.[5] Recent work[6] indicates that dogs deprived of food for seven days have much less insulin in their pancreas than do well fed dogs. It might thus be concluded that lack of dietary carbohydrate depresses the formation of insulin in the pancreas.

If restriction of dietary carbohydrate failed to induce the usual depression of carbohydrate utilization associated with organic hyper-

presented indisputable evidence that neoplastic pancreatic islet tissue, by producing excessive amounts of substance having the physiologic properties of insulin, caused spontaneous hypoglycemia. It has since been demonstrated repeatedly [2] that complete surgical removal of islet cell tumors results almost invariably in disappearance of the hypoglycemic state. Although almost 100 cases have now been reported in which pancreatic islet cell tumors, associated with clinical hyperinsulin-

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The expense of these studies was defrayed in part by a grant from the Horace H. Rackham and Mary A. Rackham Foundation.

1. Harris, S.: Hyperinsulinism, a Definite Disease Entity, J. A. M. A. **101**: 1958 (Dec. 16) 1933.

2. Wilder, R. M.; Allen, F. N.; Power, M. H., and Robertson, H. E.: Carcinoma of the Islands of the Pancreas: Hyperinsulinism and Hypoglycemia, J. A. M. A. **89**:348 (July 30) 1927.

3. Howland, G. W.; Campbell, W. R.; Maltby, E. S., and Robinson, W. L.: Dysinsulinism: Convulsions and Coma Due to Islet Cell Tumor of the Pancreas with Operation and Cure, J. A. M. A. **93**:674 (Aug. 31) 1929. O'Leary, J. L., and Womack, N.: Histology of Adenoma of Islets of Langerhans, Arch. Path. **17**:291 (March) 1934. Whipple, A. O., and Frantz, V. K.: Adenoma of Islet Cells with Hyperinsulinism, Ann. Surg. **101**:1299, 1935. Campbell, W. R.; Graham, R. R., and Robinson, W. L.: Islet Cell Tumors of the Pancreas, Am. J. M. Sc. **198**:445, 1939.

Several preliminary statements are necessary to characterize the conditions of experimentation and the subjects of these investigations. The experimental data were obtained during a period of seven months' continuous hospitalization of a patient with organic hyperinsulinism (preoperative period four months; postoperative period three months). Follow-up studies after discharge have been made at monthly intervals up to the present (three months). The patient, whose condition was misdiagnosed as epilepsy, had been having frequent attacks of convulsions for ten years prior to our studies. Of 182 determinations of blood sugar made during the preoperative period, the results of 55 ranged from 12 to 35 mg. per hundred cubic centimeters; of 86 made in the postoperative period, values for only 3 fell below 75 mg. per hundred cubic centimeters. All 3 were obtained during the course of a dextrose tolerance test, the lowest being 61 mg. per hundred cubic centimeters. At operation, four separate islet cell adenomas were removed from the pancreas. All experiments involving the use of continuous indirect calorimetry were controlled by means of identical experiments on normal subjects who prior to the experiments had been kept under the same conditions as those imposed on the abnormal subject. Additional control of the preoperative experiments, the data from which disclosed grossly abnormal metabolism, was obtained by repeating the experiments after operation. A detailed summary of the clinical data and of the operative and pathologic observations follows.

REPORT OF A CASE

A 59 year old white woman, a widow, had been in excellent health until January 1930 (almost ten years before her admission to the hospital), when "attacks" began. While in a trolley car on her way home from work at 6:30 p. m., she was roused at the end of the line by the conductor, who told her that she had been staring straight ahead and jerking her right arm. She managed to change cars and arrived home in a dazed state, perspiring profusely and having only a vague recollection of what had happened since she had left her office. She was ravenously hungry and recalled that she had had no breakfast and only a light lunch. She ate heartily and within fifteen minutes was again perfectly well. From then on she noticed that the omission, or sometimes the delay, of a meal would bring on a "nervous spell." Throughout the ten year period attacks came at the average rate of one or two a week, with increasing severity but not increasing frequency. For the first seven years most of the attacks occurred between 5:00 and 6:00 p. m., but more recently they came almost always between 10:00 a. m. and noon. There

If restriction of dietary carbohydrate failed to induce the usual depression of carbohydrate utilization associated with organic hyperinsulinism but did produce this phenomenon after removal of the abnormal islet tissue, certain hitherto unsettled problems would be clarified: (1) that depression of the rate of utilization of carbohydrate by antecedent restriction of carbohydrate is related to physiologic function of normal pancreatic islet tissue, and (2) that failure of this phenomenon in organic hyperinsulinism indicates an inability of the usual depressing influences to decrease the production of insulin. These and various other quantitative relations are reported herein. We are not aware of any other similarly controlled metabolic studies on patients with organic hyperinsulinism.

4. (*a*) Sheldon, J. M.; Johnston, M. W., and Newburgh, L. H.: A Quantitative Study of the Oxidation of Glucose in Normal and Diabetic Men, J. Clin. Investigation **16**:933, 1937. (*b*) Conn, J. W.: Interpretation of the Glucose Tolerance Test: The Necessity of a Standard Preparatory Diet, Am. J. M. Sc. **199**:555, 1940. (*c*) Sweeney, J. S.: Dietary Factors That Influence the Glucose Tolerance Test, Arch. Int. Med. **40**:818 (Dec.) 1927.

5. Dann, M., and Chambers, W. H.: Animal Calorimetry: The Metabolism of Glucose Administered to the Fasting Dog, J. Biol. Chem. **89**:675, 1930.

6. Haist, R. E.; Ridout, J. H., and Best, C. H.: Diet and Insulin Content of the Pancreas, Am. J. Physiol. **126**:518, 1939.

tonic and clonic convulsions. Attacks continued for ten to sixty minutes. The patient found that an attack could be aborted by the ingestion of food. Her weight increased from 150 to 170 pounds (68 to 77.1 Kg.) in the year previous to admission to the hospital. For several months, on arising in the morning, she experienced an occipital headache which disappeared after breakfast. A diagnosis of epilepsy was made.

On Nov. 4, 1939 she entered the University Hospital for study. Except for obesity, the physical examination revealed nothing abnormal. She was given a general diet, and two days later at 11:45 a. m. a typical attack was observed. The blood sugar level during the attack was 24 mg. per hundred cubic centimeters.

Fig. 1.—Section through the periphery of an islet cell adenoma.

The attack was quickly terminated by the intravenous administration of 5 Gm. of dextrose. After a five day period of standard dietary preparation[4b] the dextrose tolerance test gave the following results: fasting, 47 mg. per hundred cubic centimeters; one hour, 95 mg.; two hours, 47 mg.; three hours, 45 mg.; four hours, 43 mg., and five hours, 56 mg.

the first seven years most of the attacks occurred between 5:00 and 6:00 p. m., but more recently they came almost always between 10:00 a. m. and noon. There was never an attack during the night or before breakfast.

The typical attack was characterized by an "aura" of epigastric discomfort and numbness, first of the lips and then of the extremities. There followed a peculiar fixed and facetious expression of the face, complete change in personality, diplopia, beginning confusion and disorientation associated with jerking movements of all extremities and muscles of the jaw, complete loss of consciousness and generalized

Roentgenograms of the skull showed a normal pituitary fossa. The visual fields were normal. The basal metabolic rate was —7 per cent. Results of the sodium restriction test [7] revealed no evidence of decreased adrenal cortical function.

While the patient was on a diet low in carbohydrate, her fasting blood sugar values ranged from 21 to 37 mg. per hundred cubic centimeters. Except for mild headache, however, there were no attacks before breakfast. Typical attacks came on daily with clocklike regularity, between 11:15 a. m. and noon, with blood sugar values between 14 and 35 mg. per hundred cubic centimeters. A diagnosis of organic hyperinsulinism was made, and the metabolic studies were begun (see "Results").

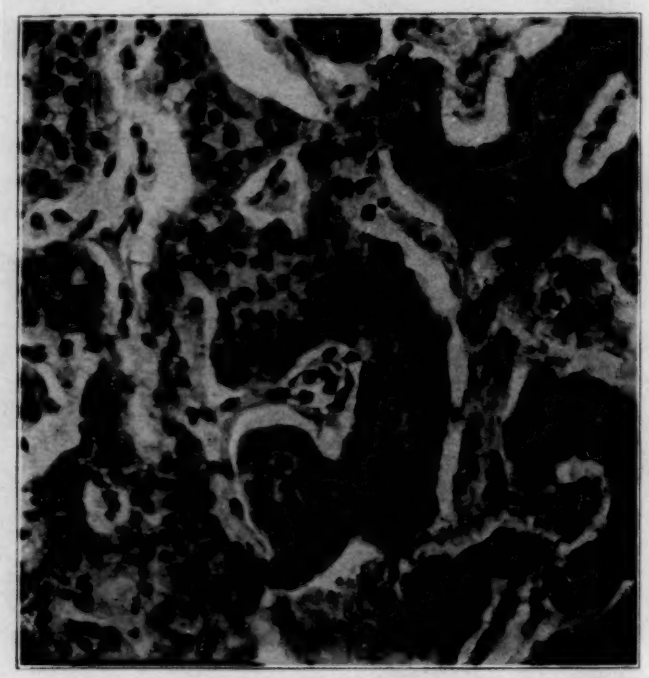

Fig. 2.—Greater magnification, showing cellular detail, of a portion of section in figure 1.

On Feb. 24, 1940 exploratory laparotomy was done by Dr. F. A. Coller. At the junction of the distal and the middle third of the tail of the pancreas a firm nodular area was felt. This area, with all the pancreas distal to it, was resected and was found to contain, deep in its substance, three separate and well encapsulated adenomas, varying from 0.5 to 1.5 cm. in diameter (figs. 1 and 2). Sections revealed another adenoma of microscopic dimensions in the same region. In the pancreatic tissue itself were areas in which the islands of Langerhans were

centimeters; one hour, 95 mg.; two hours, 47 mg.; three hours, 45 mg.; four hours, 43 mg., and five hours, 56 mg.

Hepatic function was normal, as indicated by bromsulphalein, hippuric acid and galactose tolerance tests. Levels of blood bilirubin, urinary urobilinogen and serum proteins were normal. A cholecystogram showed faint visualization, with probable stone.

markedly hypertrophic and hyperplastic (fig. 3). A specimen of the liver was taken for biopsy and for determination of glycogen content. Microscopically it appeared normal. It was noted, however, that there was a marked finely vacuolar state of the liver cells, which was not lipoidal in nature (fig. 4). This was interpreted as indicating a high content of glycogen. Chemical analysis revealed a glycogen content of 5.5 per cent. The gallbladder, which was thickened and contained several pea-sized stones, was removed.

Postoperatively a period of temporary hyperglycemia, glycosuria and ketonuria was observed. Over a period of two weeks and without the aid of exogenous insulin, the level of fasting blood sugar gradually became stabilized in the normal

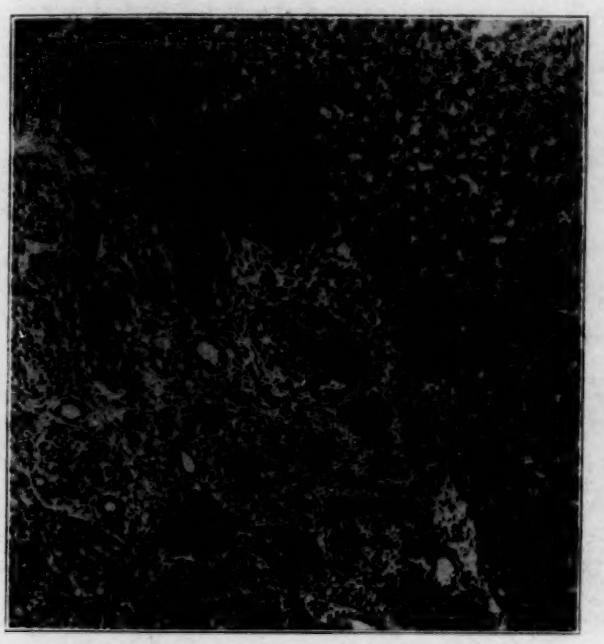

Fig. 3.—Numerous hypertrophic and hyperplastic islands of Langerhans.

range and subsequently remained there, regardless of the diet (see "Results"). Over the six months' postoperative period there has been no suggestion of hypoglycemia. The patient has returned to her daily household duties and has maintained excellent health.

METHODS OF INVESTIGATION

A respiration chamber [8] employing the principle of continuous indirect calorimetry by the open circuit method was used to obtain the data on metabolism.

8. Newburgh, L. H.; Johnston, M. W.; Wiley, F. H.; Sheldon, J. M., and Murrill, W. A.: A Respiratory Chamber for Use with Human Subjects, J.

revealed another adenoma of microscopic dimensions in the same region. In the pancreatic tissue itself were areas in which the islands of Langerhans were

7. Cutler, H. H.; Power, M. H., and Wilder, R. M.: Concentration of Chloride, Sodium and Potassium in Urine and Blood: Their Diagnostic Significance in Adrenal Insufficiency, J. A. M. A. **111**:117 (July 9) 1938.

Frequent checks of the chamber by means of the combustion of alcohol demonstrated that the method is capable of determining over 99 per cent of the gaseous exchange. Each collection of respired gases from the patient and from the control subjects covered a continuous four hour period (8:00 a. m. to noon). On the evening preceding an experiment the subject was put to bed in the chamber. The chamber was sealed and the entire mechanism was set in operation. At 8:00 a. m. the next morning the turning of two stopcocks was all that was necessary to begin the collection of a continuous sample of chamber air. Analysis of gases was done by the technic of Carpenter.[9] Carefully weighed, constant diets were used throughout all experiments. Whenever a change in the composition of the diet was

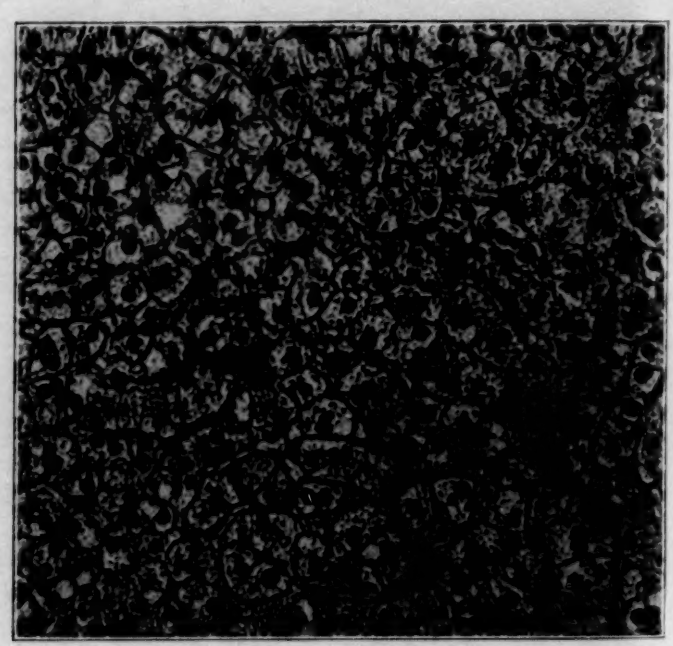

Fig. 4.—Biopsy section of the liver. Note the marked nonlipoidal intracellular granularity. The glycogen content was 5.5 mg. per hundred grams.

instituted, a period of at least five days was allowed for physiologic adjustment before the next experiment was carried out. Data on gaseous exchange were calculated in the standard way.[10] Blood sugar was determined by the Benedict

9. Carpenter, T. M.: Ein Apparat zur Analyse von Gasen aus Respirationskammern für Menschen und Tiere, in Abderhalden, E.: Handbuch der biologischen Arbeitsmethoden, Berlin, Urban & Schwarzenberg, 1937, pt. 4, sect. 13, p. 593.

10. Lusk, G.: The Elements of the Science of Nutrition, ed. 4, Philadelphia, W. B. Saunders Company, 1928, p. 61.

8. Newburgh, L. H.; Johnston, M. W.; Wiley, F. H.; Sheldon, J. M., and Murrill, W. A.: A Respiratory Chamber for Use with Human Subjects, J. Nutrition **13**:193, 1937.

method[11] and urinary nitrogen by the Kjeldahl method. Liver glycogen was determined by the method of Good, Kramer and Somogyi,[12] the specimen of liver having been frozen by solid carbon dioxide immediately on its removal from the body.

RESULTS

Convulsive Seizures.—In the preoperative period a total of fifty convulsive attacks were observed (fig. 5). Seventy-four per cent of them occurred between 11:15 a. m. and 12:50 p. m. and 14 per cent between 4:00 and 5:30 p. m. Only two attacks occurred before breakfast, although the level of blood sugar was frequently lower then than at 11:30 a. m., when a convulsion usually took place. Attacks occurred

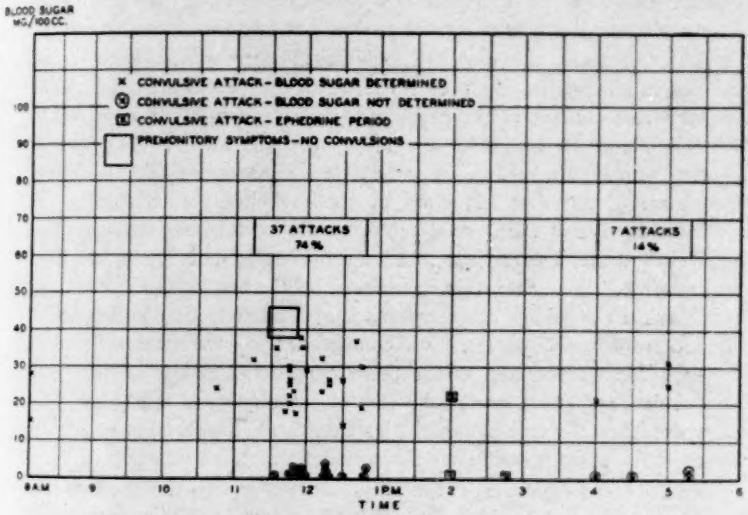

Fig. 5.—Time incidence of the fifty convulsive attacks observed.

at levels of blood sugar ranging from 13 to 38 mg. per hundred cubic centimeters. When convulsions did not appear at the expected hour, premonitory symptoms (numbness of the lips, hands and feet; visual disturbances; trembling, etc.) were extremely frequent between 11:25 and 11:50 a. m., at blood sugar levels of 38 to 47 mg. per hundred cubic centimeters.

11. Benedict, S. R.: The Analysis of Whole Blood: II. The Determination of Sugar and of Saccharoids (Non-Fermentable Copper Reducing Substances), J. Biol. Chem. **92**:141, 1931.

12. Good, C. A.; Kramer, H., and Somogyi, M.: The Determination of Glycogen, J. Biol. Chem. **100**:485, 1933.

Indirect Calorimetry.—The table summarizes the data on the patient and on the control subjects obtained from four hour periods of continuous indirect calorimetry. When prepared for five days with a diet yielding maintenance calories and containing 300 Gm. of carbohydrate and 80 Gm. of protein and when given a test dose of 60 Gm. of dextrose in the chamber on the morning of the experiment, the patient derived 97.6 per cent of her nonprotein calories from the combustion of carbohydrate and only 2.4 per cent from the oxidation of fat. Under the same conditions the controls obtained only 50 to 60 per cent of their nonprotein calories from carbohydrate and 40 to 50 per cent from fat. Thus, under these conditions, the patient gave evidence of tremendous overcombustion of carbohydrate at the expense of fat. Fifty-three days after operation the results for the patient fell into the normal range.

The conditions of the second experiment were essentially the same, the only alteration having been a change in the preparatory diet. The carbohydrate content of the preparatory diet was reduced from 300 to 100 Gm., and an isocaloric amount of fat was added. The protein content remained constant. The test dose of dextrose (60 Gm.) was the same. Note that reduction of the carbohydrate content of the preparatory diet of the normal subjects reduced the rate of combustion of carbohydrate, despite the fact that the same quantity of dextrose was presented for combustion in the form of the test dose. The patient, under these conditions, demonstrated a marked reduction in the rate of oxidation of carbohydrate. As compared with the normal level of carbohydrate combustion under these conditions, however, there was still evidence of great overcombustion of carbohydrate. Sixty-five days after operation the rate of carbohydrate oxidation appeared to be slightly subnormal. Fifteen days later the metabolic mixture was normal.

In the third experiment, the preparatory diet was the same as that used for the second (carbohydrate, 100 Gm.; protein, 80 Gm., and maintenance calories). The only variation was the elimination of the test dose of dextrose. The subjects drank an equivalent volume of water at the beginning of the four hour period in place of the usual solution of dextrose. Thus, by a comparison of results of the second and third experiment we obtained a measure of (1) the rate of postabsorptive combustion of carbohydrate when the preparatory diet had been moderately low in carbohydrate and (2) the effect per se of the ingestion of 60 Gm. of dextrose on combustion of carbohydrate. It is seen that under these conditions of dietary preparation the rate of postabsorptive combustion of carbohydrate by the patient was reduced to the normal level. The comparison of results, however, brings out a significant fact. Although under the conditions of experiment 2 both the patient and the controls oxidized carbohydrate at the same rate in the postabsorptive

Combustion of Carbohydrate, Fat and Protein
Four Hour Test Periods in Respiration Chamber

Experiment No.	Subject	Preparatory Diet (5 Days), with Maintenance Calories		Test Dose in Chamber; Dextrose, Gm.	Total Respiratory Quotient	Nonprotein Respiratory Quotient	Total Heat Produced, Calories	Heat Produced, Protein Calories	Heat Produced, Nonprotein Calories	Source of Nonprotein Calories, Percentage		Comment
		Carbohydrate, Gm.	Protein, Gm.							Carbohydrate	Fat	
1	Patient	300	80	60	0.956	0.992	267	47	220	97.6	2.4	Before operation
	Control	300	80	60	0.848	0.857	291	45	246	53.1	46.9	
	Control	300	80	60	0.863	0.876	282	45	237	59.5	41.5	
	Control	300	80	60	0.874	0.887	342	49	293	63.1	36.9	
	Control	300	80	60	0.841	0.846	378	37	341	49.3	50.7	
	Patient	300	80	60	0.865	0.872	296	28	268	58.2	41.8	53 days after operation
2	Patient	100	80	60	0.884	0.901	267	42	225	67.8	32.2	Before operation
	Control	100	80	60	0.820	0.824	327	53	274	41.7	58.3	
	Control	100	80	60	0.832	0.838	310	52	258	46.5	53.5	
	Patient	100	80	60	0.833	0.866	268	35	233	34.5	65.5	65 days after operation
	Patient	100	80	60	0.826	0.830	274	35	239	43.8	56.2	80 days after operation
3	Patient	100	80	0	0.780	0.776	253	39	214	24.9	75.1	Before operation
	Patient	100	80	0	0.794	0.792	257	41	216	30.6	69.4	Before operation
	Control	100	80	0	0.782	0.778	328	56	272	25.6	74.4	
	Control	100	80	0	0.792	0.790	336	48	288	29.9	70.1	
	Control	100	80	0	0.791	0.790	335	48	287	29.9	70.1	
4	Patient	300	80	0	0.868	0.882	250	39	211	61.5	38.5	Before operation

state, the ingestion of 60 Gm. of dextrose afforded in the patient a much greater stimulus for the combustion of carbohydrate than it did in the controls.

Two other observations must be mentioned here since they support certain conclusions. 1. Despite the fact that a low carbohydrate preparatory diet reduced the rate of postabsorptive combustion of carbohydrate by the patient to the level exhibited by the normal subjects, the blood sugar level of the patient continued to fall slowly in the four hour period without food. The blood sugar level of the controls, on the other hand, remained relatively constant. 2. The rate of postabsorptive combustion of carbohydrate by the patient when she had been previously

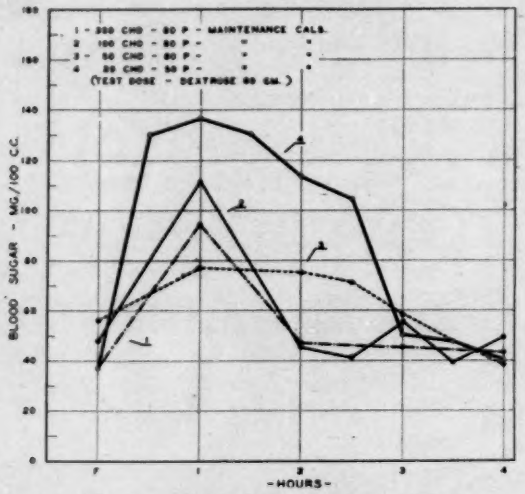

Fig. 6.—Effect of previous diet on the dextrose tolerance curve in a case of organic hyperinsulinism before surgical removal of islet cell tumors.

prepared with a higher carbohydrate diet (table, experiment 4) was as great as the rate in normal subjects prepared in the same way but given in addition 60 Gm. of dextrose (group 1). Stated differently, under conditions of high carbohydrate preparation the postabsorptive rate of carbohydrate combustion in the patient was at least as rapid as the postprandial rate in normal persons.

Dextrose Tolerance Curves.—Another experiment, dealing with the effect of variations in the carbohydrate content of the preparatory diet on the blood sugar time curve after the ingestion of dextrose, was done for the following reasons: 1. It has been shown repeatedly that manipu-

lation of the antecedent diet of a normal person produces remarkable changes in the shape of the dextrose tolerance curve. 2. All types of dextrose tolerance curves have been reported in cases of proved organic hyperinsulinism. We believe much of this confusion to be due to the lack of a standardized preparatory diet.

Figure 6 shows that the type of curve obtained in a case of organic hyperinsulinism is influenced by the composition of the antecedent diet. It should be pointed out that these differences were obtained after relatively short periods (five days) of preparation with the various diets;

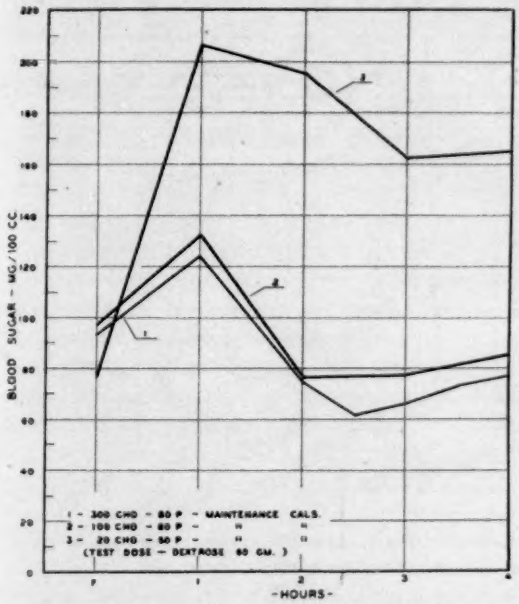

Fig. 7.—Effect of previous diet on the dextrose tolerance curve in a case of organic hyperinsulinism six months after surgical removal of islet cell tumors.

longer periods would be expected to produce even wider variations. Figure 7 shows the results of the same experiments made on the same patient six months after operation (the experiment represented by curve 3, figure 6, was not repeated). It may be seen that qualitatively the responses are the same. The degree of change, however, produced by a short period of sharp restriction of carbohydrate is greater after the normal metabolism of carbohydrate has been restored.

Observations During the Early Postoperative Period.—In figure 8 are shown data obtained in the immediate preoperative and postoperative

periods. For ten days before operation the level of the fasting blood sugar ranged from 22 to 47 mg. per hundred cubic centimeters. Twenty-four hours after operation the fasting blood sugar level was 320 mg. per hundred cubic centimeters and was accompanied by heavy glycosuria and ketonuria. No exogenous insulin was given. The ketonuria disappeared in twenty-four hours, but the glycosuria persisted for five days. The level of the fasting blood sugar fell slowly, reaching 100 mg. per hundred cubic centimeters on the seventh postoperative day. For three weeks it remained close to 100 mg. and then stabilized between 90 and 100 mg. per hundred cubic centimeters, where it has remained for

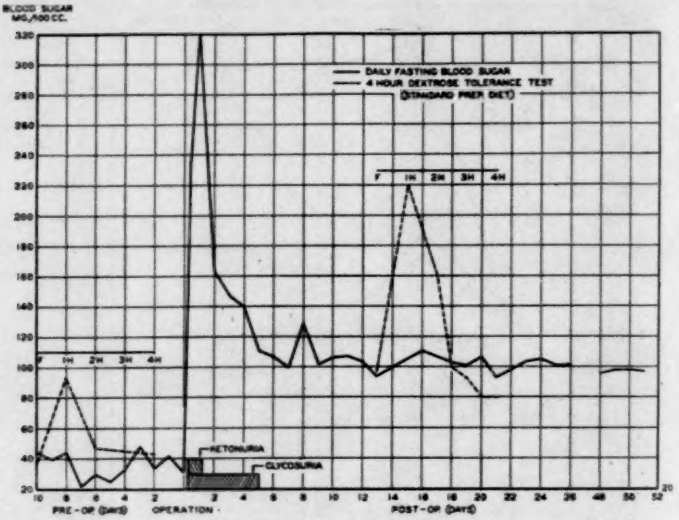

Fig. 8.—Preoperative and postoperative fasting blood sugar levels and dextrose tolerance curves in a case of organic hyperinsulinism.

the past four months. The broken lines compare a preoperative dextrose tolerance curve with an early postoperative one, both having been preceded for five days by the standard preparatory diet.

COMMENT

Organic hyperinsulinism represents only one of a great many causes of spontaneous hypoglycemia. In classifying, from the point of view of clinical behavior, the various etiologic types of spontaneous hypoglycemia one of us [13] divided them into two broad groups, namely, the

13. Conn, J. W.: Spontaneous Hypoglycemia: Classification and Principles of Treatment, in Therapeutics of Infancy and Childhood, New York, Paul B. Hoeber, Inc., to be published.

stimulative hypoglycemias and the fasting hypoglycemias. The best example of the stimulative type is that condition designated as functional hyperinsulinism, in which a precipitous fall of the blood sugar to hypoglycemic levels follows the ingestion of large amounts of carbohydrate. The level of the fasting blood sugar, however, remains normal even when dietary carbohydrate is restricted. The episodes of transient postprandial hypoglycemia are controlled by reducing the carbohydrate content of the diet. The fasting type of spontaneous hypoglycemia is well illustrated in cases of certain kinds of severe hepatic disease in which restriction of dietary carbohydrate produces a low level of the fasting blood sugar. A diet high in carbohydrate controls the fasting hypoglycemia.

Organic hyperinsulinism appears to include both of these types. A low level of the fasting blood sugar is always found, and restriction of the carbohydrate of the diet depresses it further. In this sense the condition may be classified as a fasting hypoglycemia. At the same time, however, a stimulative effect is seen in the fact that two to four hours after a meal the level of the blood sugar is frequently far below that observed in the postabsorptive state. It is thus noteworthy (fig. 5) that of fifty hypoglycemic attacks observed in the preoperative period, 74 per cent occurred in the forenoon and 14 per cent in the late afternoon. Hypoglycemia, usually asymptomatic, was always present before breakfast, but the blood sugar level was frequently lower four hours after breakfast. An active and rapid reduction of the blood sugar level in the postprandial period is, therefore, evident. The results of the studies on gaseous exchange (table) demonstrated overcombustion of carbohydrate following a test dose of dextrose, regardless of the antecedent diet. We regard these observations as evidence of an excessive stimulation by the ingestion of carbohydrate of those mechanisms involved in the rapid removal of sugar from the blood. Since all such evidence disappeared on the removal of the islet cell tumors, it seems fair to conclude that the stimulative effect had been on the islet tissue and had resulted in an excessive secretion of insulin.

In the postabsorptive state, the gradual fall of the blood sugar must be due to one of the following elements or to a combination of them; (1) abnormal withdrawal of blood sugar for storage as glycogen; (2) abnormal withdrawal of blood sugar for combustion, and (3) insufficient supply of sugar from the liver to the blood to meet the requirements of utilization of sugar. The finding of 5.5 per cent glycogen in the liver at operation when the level of fasting blood sugar on the same morning was 24 mg. per hundred cubic centimeters suggested that abnormal retention of hepatic glycogen was a factor. The demonstration that on a normal diet the rate of combustion of carbohydrate by the patient in

the postabsorptive state was markedly increased (table, experiment 4) indicates that this mechanism, too, was at work reducing the level of the fasting blood sugar. It appears, then, that the fasting hypoglycemia, obviously the result of too much insulin, is associated with both abnormal inhibition of hepatic glycogenolysis and excessive combustion of sugar.

The results obtained by indirect calorimetry [14] may be summarized in the following way: As compared with normal persons, the patient with organic hyperinsulinism who is eating an average diet derives a much greater percentage of total heat from the combustion of carbohydrate, in the postabsorptive as well as in the postprandial state. This appears to indicate a continuously excessive secretion of insulin. Limitation of carbohydrate in the antecedent diet reduces the postabsorptive rate of combustion of carbohydrate to the same level as that exhibited by normal subjects under the same conditions. But, even under these circumstances, the ingestion of dextrose results in much greater combustion of carbohydrate in a person with organic hyperinsulinism than in a normal person. This indicates an excessive responsiveness of the insulin-forming mechanism to the normal stimulus. Removal of islet cell tumors results in the restoration of the normal rate of combustion of carbohydrate under all the conditions just mentioned.

The demonstration that such a patient derives a significantly greater percentage of his total heat from the combustion of carbohydrate is not surprising. But the observation that a diet restricted in carbohydrate reduces the postabsorptive rate of carbohydrate oxidation to the normal

14. Several points regarding the information obtained by continuous indirect calorimetry are worthy of emphasis. Wilder and associates,[2] in their study of the first proved case of organic hyperinsulinism, using the technic of periodic sampling of respired gases, observed individual respiratory quotients as high as 1.06 after the ingestion of 100 Gm. of dextrose. Others (Liu, S. H.; Loucks, H. H.; Chou, S. K., and Chen, K. C.: Adenoma of Pancreatic Islet Cells with Hypoglycemia and Hyperinsulinism: Report of a Case with Studies on Blood Sugar and Metabolism Before and After Operative Removal of Tumor, J. Clin. Investigation **15**:249, 1936), using the same methods, have reported respiratory quotients approaching unity in similar cases after the administration of dextrose. Respiratory quotients which approach unity for a short period after the ingestion of dextrose can be demonstrated consistently in normal persons, the height of the respiratory quotient being a function of the antecedent diet, the amount of dextrose administered, the time of collection of gases after ingestion of dextrose and several other variables. Hence, a calculation of the total combustion of carbohydrate over a given period is not valid unless the respiratory quotient of the total respiratory exchange for the period is obtained. Continuous indirect calorimetry meets this requirement. The use of long periods of standard dietary preparation and the inclusion of normal subjects studied under the same conditions allow a quantitative comparison of carbohydrate combustion.

level requires further elucidation. At first glance, one might conclude that under conditions of low carbohydrate feeding the rate of postabsorptive liberation of insulin is reduced to the normal level. It is well known clinically, however, and it was demonstrated again in this patient, that in dealing with organic hyperinsulinism restriction of dietary carbohydrate leads to intense postabsorptive hypoglycemia. Thus, even though the combustion of sugar is not excessive, the blood sugar continues to fall to hypoglycemic levels. How, then, can one reconcile these two apparently conflicting sets of evidence?

The analysis of a specific experiment brings out the problem more clearly. During a five day period of low carbohydrate preparation for a respiration experiment the fasting blood sugar level (8:00 a. m.) averaged 52 mg. per hundred cubic centimeters (range, 45 to 65 mg. per hundred cubic centimeters). On the sixth morning a four hour chamber study of oxidation with the patient in the fasting state was made (8:00 a. m. to noon). The blood sugar at noon was 38 mg. per hundred cubic centimeters. There was, therefore, a gradual fall of the blood sugar, despite the fact that the rate of combustion of carbohydrate during the period was normal (table). Under these conditions, a mechanism other than overcombustion of carbohydrate was responsible for the gradual fall of the blood sugar. It seems likely that the rate of hepatic glycogenolysis was too slow to supply to the blood that amount of dextrose necessary to satisfy the normal rate of utilization by the tissues. The large amount of glycogen found in liver by us and by others supports this assumption. It appears, then, that in cases of organic hyperinsulinism restriction of dietary carbohydrate may reduce the rate of postabsorptive combustion of carbohydrate to the normal level but that evidence of excessive insulin activity is still manifested by an abnormal inhibition of hepatic glycogenolysis and resultant hypoglycemia. In this condition, therefore, the secretion of excessive amounts of insulin cannot be brought under control by the institution of a diet low in carbohydrate. The abnormal islet tissue seems to have acquired at least partial independence of the usual depressing influences.

The diagnostic significance of the dextrose tolerance test in cases of organic hyperinsulinism has been questioned because all types of curves have been obtained in proved cases. All types of curves can be produced in normal people,[15] as well as in those with organic hyperinsulinism (fig. 6), if one varies the amount of carbohydrate in the antecedent diet. Since in the past no attempt has been made to control the antecedent diet, it is not surprising that wide variations have occurred. We suggest that the use of a standard preparatory diet [4b] will result in much more comparable and reproducible results.

15. Conn.[4b] Sweeney.[4c]

CONCLUSIONS

When the composition of the diet is average with respect to carbohydrate, protein and fat, there is associated with organic hyperinsulinism tremendous overcombustion of carbohydrate, both in the postprandial and in the postabsorptive state. Since the normal rate of combustion of carbohydrate is restored by the removal of islet cell tumors, we regard these observations as evidence of a continuously excessive secretion of insulin.

A diet low in carbohydrate depresses the rate of combustion of a standard test dose of dextrose. As compared with the normal rate under the same conditions, however, the rate of combustion of carbohydrate in organic hyperinsulinism is still greatly increased.

In persons with organic hyperinsulinism a diet low in carbohydrate depresses the postabsorptive rate of carbohydrate oxidation to the same level as that exhibited by normal persons under the same conditions. Nevertheless, the fasting blood sugar of the former continues to fall to hypoglycemic levels while that of the latter does not.

Excessive inhibition of hepatic glycogenolysis accounts for the postabsorptive hypoglycemia occurring when the rate of combustion of carbohydrate has been depressed to the normal level by low carbohydrate feeding. The association of postabsorptive hypoglycemia with a large amount of glycogen in the liver supports this contention.

Under all conditions studied, evidence of excessive liberation of insulin has been encountered. While the rate of excessive production of insulin appears to be influenced to some degree by variations in the carbohydrate content of the diet, the liberation of insulin cannot be sufficiently depressed by low carbohydrate feeding to prevent hypoglycemia.

Variations in the type of dextrose tolerance curve produced in persons with organic hyperinsulinism by changes in the antecedent diet are qualitatively similar to variations in those produced in normal persons, but the degree of variation is less in the former. A standard preparatory diet results in much more comparable and reproducible curves.

BLOOD SUGAR IN A CASE OF COMPLETE HYPOPHYSECTOMY

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In this communication we shall show primarily that total removal of the pituitary body lowers the fasting blood sugar to a hypoglycemic level without shock and gives a delayed sugar tolerance curve, which may be a plateau at times. Furthermore, we shall show that the blood sugar level is not wholly dependent on the presence of this gland and that apparently the gland has not complete control over any vital function.

Detailed reports of the surgical procedures employed by the neurosurgeons in the removal of a pituitary tumor and the inadvertent complete removal of the hypophysis are presented with the purpose of proving our contention that no pituitary tissue remained in this case.

Our studies were considerably limited by the patient's extreme irritability and his hypersensitiveness to pain. A number of tests had to be interrupted because of the intense mental and physical reactions incurred.

REPORT OF A CASE

A. S., a 33 year old truck driver, was admitted to the New York City Hospital on April 15, 1937, having been transferred from Bellevue Hospital. His history up to about Jan. 1, 1935 was of no significance. At that time he noticed increasingly severe headaches and failing vision. He was admitted to a local hospital in April 1935, at which time a complete study showed evidence of a tumor of the pituitary body.

On March 14, 1935 incision and elevation of a bone flap, with an attempt at enucleation of the tumor, were carried out. The operative report was as follows: "Beneath the chiasm, and apparently pushing it upward, was a slightly reddish tumor, approximately 2 cm. in diameter, resting within the pituitary fossa. Incision into the visible portion of the tumor was made, and curettement was then done with a pituitary spoon; a considerable amount of exceedingly soft tissue was recovered in small fragments. Eventually a cavity was formed in the tumor mass, large enough to admit two full-sized cotton pledgets. It was deemed wise to discontinue further surgical attempts at ablation and to depend on roentgen therapy."

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On April 10 the patient returned to the operating room for reelevation of the bone flap and removal of a meningioma of the sella turcica. The operative report read as follows: "The left optic nerve and the left half of the optic chiasm were visible, as was the opening made into the capsule of the tumor underneath the optic chiasm and leading down into the sella, presumably into a cavity within the tumor. The right half of the optic chiasm and the right optic nerve and part of the optic tract lay partly underneath this tumor mass and partly enclosed within it, so that the left end of the chiasm lay superior to the tumor while the right end lay inferior to it. The tumor was removed bit by bit from these nerves until finally they were exposed in toto, the chiasm being badly damaged. It was then possible to free the tumor down to the sella. A flat blade endothermy tip was pushed within the sella and the coagulation current turned on. Tissue thus treated appeared to shrink under the eye. The capsule of the tumor actually pulled away from the walls of the sella, leaving them free and glistening. By means of sytemic coagulation, traction and blunt and sharp dissection, it was finally possible to remove all the tumor from the pituitary fossa, leaving the floor of the fossa smooth and glistening. The actual attachment of the tumor was never determined with certainty, but was probably the tuberculum of the sella. This region was thoroughly cauterized to prevent any local recurrences."

The report of the microscopic examination of the material removed, stated: "The tissue is composed chiefly of epithelial cells, polyhedral and closely packed, with a suggestion of arrangement in columns; the nuclei are compact and the fairly abundant cytoplasm varies from basophilic to pituitary gland cells." A second report mentioned "fibroblastic proliferation with calcific deposits and meningeal hyperplasia, possibly meningioma."

Recovery was uneventful; headaches were relieved, and vision was improved. However, abdominal cramps developed, and the patient was admitted to Bellevue Hospital on Jan. 24, 1937.

On April 15, 1937, when he was transferred to New York City Hospital from Bellevue Hospital, he gave the appearance of a prematurely aged, extremely emaciated man, with fine dry skin, high-pitched voice and feminine distribution of hair. Examination revealed severe abdominal cramps and failing vision. The fundi showed second degree atrophy of the optic nerves and bilateral hemianopia, with loss of visual acuity. There was marked hyperesthesia to touch over the abdomen; no mass was palpable. The blood pressure was 100 systolic and 68 diastolic.

The course of his illness at the City Hospital has been stationary. Treatment has been based on substitution and on symptomatic needs. During the greater part of his stay he has received 6 grains (0.39 Gm.) of whole pituitary and 2 grains (0.13 Gm.) of thyroid daily.

On examination on Oct. 1, 1940, at which time he was a bed patient, he was undernourished and constantly cried out as if in distress. There was rotary nystagmus of both eyes; the disks were barely visible but were normal, and there was poor vision in the right eye, with practically complete blindness in the left. The right arm and hand and both legs were contracted. There were atrophic changes of the skin of the legs and feet, with ulcers. He suffered severely with hyperesthesia and hyperalgesia over the whole body. So extreme was his condition that we hesitated to carry on too exacting an examination.

Roentgenograms of the long bones yielded the following information: "The proximal half of the right radius shows destruction of the cortex along the interosseous border. The bone has an irregular appearance, the result of an osteoid

reaction. The cortex is defined and shows localized areas of thinning and thickening throughout the roentgenograms. The bones forming the right knee joint and the right ankle have undergone decalcification secondary to disuse. The left knee and ankle show similar changes. The head of the left femur is partially destroyed."

The laboratory findings during the patient's stay in the hospital were as follows: urine, essentially normal; Wassermann reaction, negative; nonprotein nitrogen, 27 to 29 mg. per hundred cubic centimeters; icteric index, 6; basal metabolic rate, —7 to —29 per cent; blood chlorides, 353 to 512 mg. per hundred cubic centimeters; blood phosphates, 2.2 to 3.3 mg. per hundred cubic centimeters; blood urea nitrogen, 14.9 mg. per hundred cubic centimeters, and blood cholesterol, 138 to 266 mg. per hundred cubic centimeters. Electrocardiograms were essentially normal. An average blood count revealed 4,000,000 red cells and 7,200 white cells, with a normal differential count; the hemoglobin content was 11 Gm. per hundred cubic centimeters.

The fasting blood sugar on admission was 80 mg. per hundred cubic centimeters. Another determination a little later gave a value of 45 mg. A sugar tolerance test made on Oct. 13, 1938 yielded the following data: fasting, 34 mg.; one-half hour, 65 mg.; one hour, 98 mg.; two hours, 118 mg., and three hours, 34 mg. On June 28, 1939 samples of blood were taken one hour before and one hour after eating, and the sugar content was reported as 66 and 69 mg., respectively, per hundred cubic centimeters. On April 4, 1940 another sugar tolerance test gave the following results: 66, 111, 125, 111 and 108 mg. On Aug. 8, 1940 we began another test but were forced to discontinue it before it was completed. The fasting, half-hour and one hour values were 46, 70 and 76 mg., respectively.

COMMENT

We believe that the operative reports in this case furnish evidence that a complete hypophysectomy was performed. It is reasonable to assume that complete cleaning out of the sella turcica, such as was done in this case, means that the whole pituitary gland was removed. With the acceptance of this fact, therefore, we are justified in concluding that the pituitary body is not a vital organ. For a number of years it has been taught that the hypophysis is essential to life.[1] This concept, however, has not been universally accepted. Paulesco, in 1907, first succeeded in both partially and completely extirpating the pituitary in dogs and pronounced this gland a vital organ. Later Cushing, Bell and Beidl and their co-workers, using the same technic, concurred with Paulesco in the belief that the pituitary was essential to life. Van Dyke,[2] in a review of the recent work done on this subject, covering over 500 manuscripts, maintained that the pituitary is by no means a vital

1. Boyd, W.: Physiology of the Pituitary Body, in A Textbook of Pathology, Philadelphia, Lea & Febiger, 1932, p. 704. Towne, E. B.: The Pituitary Body, in Nelson New Loose-Leaf Medicine, New York, Thomas Nelson & Sons, 1938, vol. 3, pp. 239-256. Cushing, H.: The Pituitary Body and Its Disorders, Philadelphia, J. B. Lippincott Company, 1912.

2. Van Dyke, W. E.: Physiology and Pharmacology of the Pituitary Body, Chicago, University of Chicago Press, 1936, pp. 1-56.

organ. He claimed that most workers performing extirpation experiments have failed to take into consideration injury to the brain, which is always an accompaniment, owing to the intimate relation of the pituitary to the hypothalamus. Dandy and Reichert,[3] in their experiments on dogs, likewise came to the conclusion that there was "no evidence to support and every evidence to refute the assumption that the hypophysis is essential to life." They used the transbuccal approach rather than the elevation of a bone flap and kept some of their dogs alive almost three years after complete extirpation of the gland. Baker and Craft[4] reported the case of an 18 year old pituitary dwarf studied over a period of eight years who died after an appendectomy. Autopsy showed that only about one sixth of the normal number of anterior lobe cells remained, while changes in the posterior lobe were even more striking in that there was complete replacement by connective tissue of all normal elements. Most of the connective tissue had undergone hyalinization, so that no normal posterior lobe could be identified.

We found that the fasting blood sugar values in our case were well within the hypoglycemic range. All told, there were six reports on fasting blood sugar; the lowest value was 34 mg. per hundred cubic centimeters, and the highest was 80 mg. The average of the six values was 57 mg. It will be noted that shock was not present when these readings were made. This is in accord with the observations of Hart and Lisa[5] that fasting blood sugar values within the hypoglycemic range without any evidence of shock are common.

Four dextrose tolerance tests were performed. Two standard curves were completed. These might be interpreted as delayed curves. A third standard curve was incomplete, but what was present could be classed as low plateau. The remaining test, which was made to show the effect of a meal, revealed little or no rise one hour after the food had been ingested. One could say from the results that the response to dextrose was somewhat erratic, with, however, a tendency toward a delayed rise in the tolerance curve and, at times, a low plateau. Because the blood sugar remains within certain levels, neither disappearing from the blood stream nor reaching diabetic values, and because the values change after the ingestion of dextrose, it is apparent that the blood sugar levels are not wholly dependent on the pituitary.

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3. Dandy, W. E., and Reichert, F. L.: Experimental Hypophysectomy in Dogs, Bull. Johns Hopkins Hosp. **62**:122-156, 1938; Studies on Experimental Hypophysectomy: Effect on the Maintenance of Life, ibid. **37**:1-13, 1925.

4. Baker, A. B., and Craft, C. B.: Bilateral Localized Lesions in the Hypothalamus with Complete Destruction of the Neurohypophysis in a Pituitary Dwarf with Severe Permanent Diabetes Insipidus, Endocrinology **26**:801-807, 1940.

5. Hart, J. F., and Lisa, J.: The Rate of Occurrence of Hypoglycemia, Endocrinology **27**:19-22, 1940.

Lawrence and Hewlett [6] stated that the pituitary gland acts solely as a stabilizer of the blood sugar. This is within reason; yet there seems to be a blood sugar level–raising mechanism involved.

CONCLUSIONS

1. The total removal of the hypophysis produces a drop in the fasting blood sugar to hypoglycemic levels.

2. No shock accompanies these low values.

3. Sugar tolerance curves are somewhat erratic, with a tendency to a delayed rise and, at times, a plateau.

4. The level of the blood sugar is not wholly dependent on the pituitary gland.

5. The pituitary gland functions as a blood sugar level–raising mechanism.

6. The pituitary gland is not a vital organ.

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6. Lawrence, R. D., and Hewlett, R. F. L.: Effect of Pituitrin and Insulin on Blood Sugar, Brit. M. J. **1**:998-1002, 1925.

BIOLOGIC FALSE POSITIVE SEROLOGIC REACTIONS IN TESTS FOR SYPHILIS

I. OCCURRENCE IN NORMAL PERSONS

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Opinion as to the specificity of serologic tests for syphilis, since their first introduction in 1906, has passed through two periods and is well on its way into a third. For the first ten to fifteen years it was generally thought that positive results might occur in relation to many diseases other than syphilis, and there is a vast literature reporting "false positive" reactions in cases of almost every known disease. In the following two decades the pendulum swung in the reverse direction. It was generally felt that, except for the results in yaws, leprosy, malaria, infectious mononucleosis and perhaps one or two other conditions, serologic tests for syphilis were amazingly specific. Technical errors excluded, when positive results were obtained either in the case of an apparently normal person or in the case of one with a clearly nonsyphilitic disease, these results were regularly assumed to be due to associated asymptomatic syphilitic infection.

In more recent years doubt has again been thrown on the specificity of serologic tests for syphilis. There is now considerable evidence not only that positive results may be produced with varying frequency by a number of diseases other than syphilis but that even nonsyphilitic, clinically normal persons may occasionally yield serums that give biologic false positive reactions. These points have become especially important with the increasingly widespread use of routine serologic tests, not only as a diagnostic measure in cases of illness but as a compulsory public health measure in premarital and prenatal examinations and in the testing of industrial personnel.

The question of biologic false positive reactions in serologic tests for syphilis will therefore be considered in three papers. This, the first

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of the series, considers their occurrence in normal persons; the second [1] discusses their incidence in patients with diseases other than syphilis; the third [2] presents a tentative method of approach to the recognition of their nonspecificity.

At the outset, a clear distinction must be drawn between technical and biologic false positive results in these tests. Technical false positive results, as the term implies, are those due to one or more of many possible technical errors in the performance of the test, and are not found in repeated tests on the same serum by the same or different technics in the same or different laboratories. Included in the category of technical false positive results should probably be certain of those obtained with supersensitive flocculation technics, such as the Kline exclusion or the Kahn presumptive test, even though these results may be repeated with the same serum and the same technic in the same or different laboratories. In these supersensitive technics, specificity has deliberately been sacrificed in order to achieve maximum sensitivity, and in various serologic surveys these "screen" procedures have given up to 10 per cent or more false positive results for normal persons. It seems probable that these false flocculation reactions depend primarily on the known instability of the particular lipoidal suspensions used as antigen.

Biologic false positive reactions, by the definition of these papers, are those for which technical error can be excluded by verification in the same or in different laboratories and in which the demonstration of a positively reacting substance in the serum rests on technics other than the supersensitive flocculation tests referred to in the foregoing paragraph.

THE LITERATURE

That reagin or a reagin-like substance might be present, either intermittently or constantly, in the serums of some normal human beings was forcibly brought to the attention of clinicians by the demonstration of the fact that such a substance is present in the serums of many other normal animals. This is not a new observation, as the fact itself has been known since 1907, but the earlier papers describing it have until recently attracted little attention, either from clinicians or from serologists. Kemp, Fitzgerald and Shepherd [3] have completely reviewed the

1. Mohr, C. F.; Moore, J. E., and Eagle, H.: Biologic False Positive Serologic Reactions for Syphilis: II. Tests of Patients with Organic Diseases Other Than Syphilis, Arch. Int. Med., to be published.

2. Moore, J. E.; Eagle, H., and Mohr, C. F.: Biologic False Positive Serologic Tests for Syphilis: III. A Suggested Method of Approach to Their Clinical Study, J. A. M. A. **115**:1602 (Nov. 9) 1940.

3. Kemp, J. E.; Fitzgerald, E. M., and Shepherd, M.: The Occurrence of Positive Serologic Tests for Syphilis in Animals Other Than Man, with a Review of the Literature, Am. J. Syph., Gonor. & Ven. Dis. **24**:537 (Sept.) 1940.

literature pertaining to positive reactions in serologic tests for syphilis on animals other than man and have presented original observations on specimens from chickens, pigeons, rabbits, mice, cattle, sheep, horses and swine. They concluded:

> Personal experience and a review of the literature show that a large number of animals other than man have been found to have positive serologic tests for syphilis. Our findings, using a variety of tests for the examination of the sera of numerous animals, are in agreement with those of other observers. Our findings also confirm earlier observations that there is marked discrepancy between the results of the different tests in different animal species and the results of identical tests in the same animal species. Quantitative determination of the amount of reacting substance in the blood of animals shows that, as determined by the Eagle microflocculation test, it is less in amount than in the serum of known syphilitics. In two animal species, dogs and cattle, and probably sheep as well, the number of positive tests increased with increasing age of the animals.

The possibility that the serum of man, like that of other animals, might contain reagin or some reagin-like substance in the absence of syphilitic infection has of course not escaped the attention of serologists, though little stress has been laid on it. Browning,[4] Meinicke[5] and Hinkleman[6] have all contended that the difference between normal and syphilitic human serum is merely one of degree, and not of kind, and in that connection have stressed the nonspecific nature of the lipoidal "antigen" and of the "reagin" with which it combines. The more recent demonstration by Eagle[7] that the physical mechanism of the Wassermann and flocculation tests for syphilis is precisely that of specific antigen-antibody reactions, and the further demonstration by Beck[8] and by Eagle and Hogan[9] that syphilis reagin itself is probably an antibody to Spirochaeta pallida which happens to cross react with tissue lipoids, may help clarify the *raison d'être* of these tests but does not exclude the possibility that a substance reacting in a manner similar to this antibody may occasionally be present in the serum of normal

4. Browning, C. H.: Biochemistry of Immune Reactions, Brit. M. J. **1**:239, 1915.

5. Meinicke, E.: Zur Theorie und Methodik der serologischen Luesdiagnostik, Deutsche med. Wchnschr. **45**:178 (Feb. 13) 1919.

6. Hinkleman, A. J.: Biochemistry of the Wassermann Reaction, Am. J. Syph., Gonor. & Ven. Dis. **11**:594 (Oct.) 1927.

7. Eagle, H.: Studies in the Serology of Syphilis: I. Mechanism of the Flocculation Reactions, J. Exper. Med. **52**:717 (Nov.) 1930; II. The Physical Basis of the Wassermann Reaction, ibid. **52**:739 (Nov.) 1930.

8. Beck, A.: The Role of the Spirochaete in the Wassermann Reaction, J. Hyg. **39**:298 (May) 1939.

9. Eagle, H., and Hogan, R. B.: On the Presence in Syphilitic Serum of Antibodies to Spirochetes: Their Relation to So-Called Wassermann Reagin and Their Significance for the Serodiagnosis of Syphilis, J. Exper. Med. **71**:215 (Feb.) 1940.

human beings in concentration sufficient to give a positive result in a Wassermann, flocculation or even spirochetal complement fixation test.

The experimental evidence that normal human serum may contain reagin or a reagin-like substance is summarized in the following paragraphs.

In 1931 Malloy and Kahn [10] observed that when normal serum was mixed with standard Kahn antigen, microscopic aggregates formed slowly. No aggregates were visible when the mixture was examined immediately; after the mixture had stood one hour, the average size of the aggregates was 60 square microns, and after it had stood six hours, 190 square microns. In contrast, the average size of the aggregates formed by mixing syphilitic serum with standard Kahn antigen was 420 square microns when the mixture was examined immediately, 1,730 square microns after the mixture had stood one hour and 4,260 square microns after it had stood six hours. When normal serum was mixed with a sensitized antigen (that used in the Kahn presumptive test) and the mixture examined immediately, the aggregates measured on the average 40 square microns; after one hour they measured 470 square microns, and after six hours, 1,010 square microns. Corresponding figures for a mixture of syphilitic serum and sensitized antigen were 425, 1,020 and 3,160 square microns. The authors concluded:

> It is evident from these experiments that nonsyphilitic serums also show aggregates after contact with antigenic suspension. It appears that the difference between nonsyphilitic and syphilitic serums is one of degree rather than of kind—quantitative rather than qualitative. In syphilis, there seems to be a marked increase in the property possessed by nonsyphilitic serum to aggregate the lipoid particles of the antigenic suspension. When the results obtained with the two antigens are compared, the averages of the extent of aggregation are higher with standard antigen than with sensitized antigen in the case of syphilitic serums, while the reverse is true in the case of nonsyphilitic serums.

In 1934 Schreus and Foerster [11] described a method for the demonstration of small quantities of reagin in the serums of syphilitic patients whose Wassermann reactions were negative. When subliminal amounts of a serum of known positive titer, less than would be necessary to give a positive Wassermann reaction, were added to the apparently negative serums, the latter gave positive results, presumably because of an additive effect. The following year Barnett, Jones and Kulchar,[12] using the Kline

10. Malloy, A. M., and Kahn, R. L.: The Ultramicroscopic Precipitation Reaction in Syphilis, J. Infect. Dis. **48**:243 (March) 1931.

11. Schreus, H., and Foerster, R.: Spezifische Sensibilisierung von serologischen Reaktionen: Grundlage und Methodik der spezifisch sensibilisierten Wassermann-Reaktion (WSR.), Ztschr. f. Immunitätsforsch. u. exper. Therap. **82**: 53, 1934.

12. Barnett, C. W.; Jones, R. B., and Kulchar, G. V.: Measurement of Reagin in Nonsyphilitic Sera, Proc. Soc. Exper. Biol. & Med. **33**:214 (Nov.) 1935.

test, adapted this technic to the demonstration of reagin in normal serums. They concluded:

> Reagin is evidently present in the sera of non-syphilitic individuals. There is no proof that this reagin is identical with that found in syphilitic sera but is reacts in the same way to the Kline precipitation test. The difference between syphilitic and non-syphilitic sera seems to be a quantitative rather than a qualitative one.

We have repeated the experiments of Barnett and his collaborators, and are able to confirm their observation that normal serum contains a substance that will react with the antigen used in the Kline test. Although our own experiments, to be reported in a following paper, indicate that this normal reagin differs qualitatively from that of syphilitic serum, it nevertheless seems clear that the reactive factor of normal serum is a potential source of error, certainly for the Kline test, and perhaps for other flocculation tests as well.

Sherwood and his associates [13] have developed a technic which they designate as the "widespread Kahn test." A series of tubes is set up in which the serum: antigen ratio varies from 1:100 to 1:5, as compared with the ratios of 1:12 to 1:3 used in the standard diagnostic test. Serums from normal persons are sometimes found to be positive with the higher serum: antigen ratios (1:100 to 1:40), though negative with lower ratios as used in the diagnostic Kahn test and negative with all other standard diagnostic tests. Sherwood and his co-workers found this phenomenon in 12 of 1,018 serums from healthy white college students. The implication that these serums contain a reactive factor resembling that of syphilitic serum requires no discussion.

More recently Eagle [14] has approached the problem afresh from a clinical-statistical point of view. In order to estimate the probable incidence of biologic false positive reactions in the tests of normal persons, he selected a large population in whom the incidence of syphilis might properly be assumed to be very small because of age, social and educational status and other factors, i. e., white university students, both male and female. The serums of 40,545 students from twenty-five universities in various parts of the United States were examined. When positive results were obtained, the patients were carefully examined by physicians of the various student health services. An earnest effort was made, by means of careful history taking, physical examination and, often, examination of other members of the family, to determine whether

13. Sherwood, N. P.; Bond, G. C., and Canuteson, R. I.: On the Possible Presence of a Reagin-Like Factor in Normal Human Serum, Am. J. Syph., Gonor. & Ven. Dis. **25**:179 (March) 1941.

14. Eagle, H.: On the Specificity of Serologic Tests for Syphilis as Determined by 40,545 Tests in a College Student Population, Am. J. Syph., Gonor. & Ven. Dis. **25**:7 (Jan.) 1941.

the positive results obtained were due to (1) technical error, (2) syphilitic infection or (3) the factor in normal serum which gives biologic false positive results in such tests. Among the 40,545 students, the initial tests showed positive results for 73, doubtful for 117. Thirty-three of the positive and 95 of the doubtful results could be dismissed as due to technical error, since the reactions to succeeding tests were always negative and these students showed no evidence of syphilis. Twenty-six of the students with positive and doubtful results were shown to have syphilis. There remained, however, 36 students with repeatedly positive or doubtful results for whom there was neither history nor physical or collateral evidence of syphilitic infection and whose reactions might be regarded as of the biologic false positive type. This is an incidence of 1 false positive reactor in every 1,125 students tested. However, those universities with the highest incidence of syphilis also had the highest incidence of apparent biologic false positive results. Correcting statistically for this fact, Eagle estimated that with present day serologic tests the incidence of biologic false positive results in tests on the population studied is of the general magnitude of 1 for every 4,000 persons tested, and perhaps even less.

Eagle quite properly suggested that from the standpoint of public health the low incidence of biologic false positive results observed in his series creates no problem and that it is perhaps justifiable from this point of view to regard all persons with positive serum reactions as syphilitic and to treat them as such. He agrees, however, that from the point of view of the individual patient such an attitude is sometimes not justifiable. The diagnosis of syphilis has many serious implications, social, mental and physical, and antisyphilitic treatment is not without danger to health, or even life, to say nothing of its inconvenience and expense. The discovery of a positive serologic reaction for syphilis in a case in which there is no history of infection or physical evidence of this disease is therefore one which calls for the utmost care in determining the validity of the result.

That apparently normal persons may temporarily or permanently possess reagin or a reagin-like substance in their bloods which reacts positively in standard serodiagnostic tests for syphilis is shown by the following case reports. The persons concerned have all been observed in the private practice of one of us (J. E. M.). They have been studied by the methods outlined in the third paper of this series,[2] though it must be emphasized that all of the procedures there advised have not been employed in any one case, since to include them all was usually neither necessary nor feasible.

REPORT OF CASES

CASE 1.—A white man aged 28, an attorney, was required by his employer to have a yearly physical examination. In the course of the examination, on Jan.

7, 1936, he was found to have a positive reaction for syphilis. There was no history of syphilitic or gonococcic infection. On detailed physical examination there was no evidence of acquired or congenital syphilis. At no time had the patient received antisyphilitic treatment. There was no evidence of any other infectious disease. The only abnormal physical findings were small varicose veins of the right leg, leukoderma of the penis, present since childhood, and flat feet. With the exception of the serologic reaction for syphilis, the results of routine laboratory studies were negative. Particularly was there no evidence of infectious mononucleosis or malaria. The patient's mother denied having had syphilitic infection, and her reactions to serologic tests were entirely negative. The serologic tests are summarized in table 1. This patient's blood was tested in five different laboratories, and according to four of them a small quantity of reagin was present over a seven week period. Eleven weeks and again three years after the first visits the reactions were negative, and the patient remains well. No treatment was given.

TABLE 1.—*Serologic Tests for Syphilis, Case 1* *

Date	Laboratory	Wassermann	Kahn Standard	Eagle Macroflocculation	Eagle Microflocculation	Kline Diagnostic	Hinton
1/ 7/36	1	0	P	..	..	..	..
2/ 2/36	2	0	D	D	..	..	..
	3	D	..	..	D	..	..
2/ 3/36	2	0	D	D	..	..	..
	3	0	..	..	0	..	..
2/22/36	4	0	..	..	..	..	0
	5	..	..	..	..	P (3 units)	..
2/24/36	5	..	..	..	..	P	..
4/22/36	2	0	0	0	..	..	..
4/ 3/39	2	0	0	0	..	..	..

* In this table and in subsequent tables, laboratories are designated as 1, 2, 3, etc. Results of serologic tests are expressed as positive (P), doubtful (D), negative (0) and anticomplementary (A.C.). If a quantitative titration in a positive test was performed the titer, expressed in units of reagin (serum dilution), is parenthetically inserted after the positive result.

CASE 2.—A white man aged 25, a clerk, presented himself to his local physician in January 1937 for a premarital examination. At the time of this examination he was found to have a positive Wassermann reaction. The patient was seen by one of us (J. E. M.) on March 13. He denied having had gonorrhea or any lesions suggestive of syphilis. He admitted only one sexual exposure, five years before the present examination. After this exposure he had had six serologic tests for syphilis over a period of five years, all of which gave negative results. The patient had no subjective or objective signs or symptoms of syphilis at the time of examination, nor had he any signs or symptoms of any other organic disease. About five weeks prior to the examination the patient had been circumcised, and there was still slight induration in the circumcision scar. In 1934 he had malaria, which was adequately treated, and apparently there had been no recurrences. The results of the routine laboratory studies, with the exception of those in the serologic tests for syphilis, were entirely negative. A careful search was made for malarial parasites, but none could be found. (Even if a patient were a chronic carrier of undemonstrable malarial parasites, there is no information available in the literature

or in our own experience to indicate that this symptomless carrier state can produce false positive serologic results in tests for syphilis. Indeed the available evidence indicates that false positive serologic reactions in cases of malaria occur only during or shortly after the acute febrile illness.) A test for heterophil antibody gave a negative result. Complement fixation tests with gonococcus, staphylococcus and streptococcus filtrates were all positive. Especial emphasis is directed toward this nonspecific tendency to positive complement fixation with widely varying antigens. The serologic tests for syphilis are summarized in table 2.

A "provocative" injection of neoarsphenamine, 0.6 Gm., was given on March 13, 1937, but no other antisyphilitic treatment. During the first three months of 1937 this patient's blood was tested in five different laboratories by three different technics. Reagin was constantly present in small quantities during this period,

TABLE 2.—*Serologic Tests for Syphilis, Case 2*

Date January 1937 (several tests done elsewhere)	Laboratory	Wassermann P on 3 occasions in 2 different laboratories	Kahn Standard P once, D 4 times in 3 different laboratories	Eagle Macroflocculation	Eagle Microflocculation
3/13/37	1	P	0	D	..
	2	D	..	..	D
	3	D	..	..	D
3/15/37	1	P (2.5 units)	..	D	..
3/17/37	1	0	D	D	..
	2	0	..	..	0
3/18/37	1	0	D	D	..
	2	0	..	..	0
3/19/37	1	P (2.0 units)	D	D	..
	2	P (12.0 units)	..	..	P
3/20/37	1	P (2.5 units)	D	D	..
	2	P (18.0 units)	..	..	P
3/21/37	1	P (2.5 units)	..	..	P
	2	P (18.0 units)	..	..	..
3/24/37	1	0	0	0	..
	2	D	..	..	D
2/22/38	1	0	0	0	..
5/15/39	1	0	0	..	..

and there was an apparent "provocative" rise in the reported titers from one laboratory following the injection of neoarsphenamine. Eventually the reagin disappeared, and two years later the patient was well and his serum still gave a negative reaction.

CASE 3.—A white man aged 38, a physician, volunteered, about Nov. 1937, to give blood for experimental work which was being done on a new flocculation test. The serum was found to give a positive reaction with this test, and therefore the result was checked with standard tests. In the standard tests the serum gave either positive or doubtful results. The patient denied having had premarital or extramarital exposure and gave no history of primary or secondary syphilitic lesions. He had had several serologic tests for syphilis performed while he was in college and medical school, all of which gave negative reactions. He did state, however, that in May 1937, while cleaning a syringe and needle after venipuncture, he stuck the needle under his finger nail. There resulted a sore which did not heal for two weeks. This lesion contained pus and was painful. The patient did not know the

serologic status of the person on whom he did the venipuncture. There were no subsequent lesions which might have been significant. At the time of examination, Nov. 6, 1937, there were no subjective or objective signs or symptoms of syphilis, nor were there any signs or symptoms of any other organic disease. The routine laboratory studies gave negative results. A lumbar puncture was performed, and the cerebrospinal fluid was entirely normal. A test for heterophil antibody gave a negative reaction. Examination of the patient's wife, with whom he had had unrestricted sexual intercourse during the time when, if he had had early syphilis, the disease might have been expected to be most infectious, gave wholly negative results. The serologic tests are summarized in table 3. Small quantities of reagin were constantly demonstrable in six different laboratories by seven different technics over a period of six months. Since in the recent past repeated serologic tests had given negative results, the positive results appearing in the fall of 1937,

TABLE 3.—*Serologic Tests for Syphilis, Case 3*

Date	Laboratory	Wassermann	Kahn Standard	Eagle Macroflocculation	Eagle Microflocculation	Hinton	Kline Diagnostic	Laughlen
11/ 6/37	1	D	..	..	D	..	..	P
	2	D	P	D	..	..	..	..
	3	0	D	..	..	..	..	..
11/18/37	1	P (8 units)	..	..	..	..	..	..
	2	0	D	D	..	..	..	..
11/24/37	2	0	D	0	..	..	..	..
12/ 1/37	1	P	..	..	P	..	..	..
12/ 8/37	1	0	..	..	0	..	..	..
	2	P (2 units)	P	P	..	..	..	..
12/14/37	2	P (1 unit)	P	P	..	..	..	..
12/16/37	2	P (1 unit)	P	P	..	..	..	..
12/17/37	2	P (1 unit)	P	P	..	..	..	..
12/18/37	2	P (1 unit)	P	P	..	..	..	..
12/30/37	2	P (1 unit)	P	P	..	..	..	..
2/ 2/38	4	..	..	..	..	..	D	..
	5	P	D	..	..	..	D	..
	6	..	..	..	..	P	..	..
2/20/38	2	P (1.5 units)	P	D	..	..	..	..
4/20/38	2	P (1.5 units)	D	P	..	..	..	..

if due to syphilis, should have represented an early stage. One might, therefore, expect the serum titers to be consistently high, instead of, as actually observed, constantly low over a six month period without treatment.

CASE 4.—A white woman aged 25, single, consulted a physician in June 1931 because of abdominal pain. At the age of 10 she had had several sexual exposures with a 14 year old boy. The patient had not had intercourse since that time. She had no subjective or objective signs or symptoms of acquired or congenital syphilis, nor had she any signs or symptoms of any other organic disease. No organic basis could be found for the abdominal pain except that the patient was somewhat nervous and undernourished. The patient's mother denied having had syphilitic infection, and Wassermann, Kahn and Eagle tests performed on the mother's serum gave negative results. All routine laboratory studies made on the patient gave negative results with the exception of the serologic reactions for syphilis. The Wassermann tests were unusual inasmuch as those made with dilutions between 1:5 and 1:80 gave

on most occasions positive or doubtful results, whereas all those made with dilutions lower and higher than these were negative. Complement fixation tests were performed with a cholesterolized extract of sheep cells and a cholesterolized extract of milk. With both of these nonspecific antigens the serum reacted positively, and the same zone phenomenon was seen as with specific antigens. The serologic tests for syphilis are summarized in table 4. The discrepancy between the reactions to the several serologic tests for syphilis, the positive results obtained with wholly nonspecific

TABLE 4.—*Serologic Tests for Syphilis, Case 4*

Date	Laboratory	Wassermann	Kahn Standard	Eagle Macro-flocculation
6/11/31	1	P	P	0
6/12/31	1	P (1:2 to 1:100)	0	0
	2	P (1:5 to 1:64)	0	0
6/17/31	1	P (22 units)	0	0
6/20/31	1	P	0	0
	2	P	0	0
	3	0	..	..
	4	D in dilution 1:5	..	..
6/21/31		Neoarsphenamine 0.6 Gm. as provocative		
6/22/31	1	P	..	..
6/23/31	1	D in dilutions 1:5 to 1:30	..	..
6/25/31	1	D in dilutions 1:10 to 1:20	0	0
6/27/31	2	D in dilutions 1:10 to 1:80	0	0
6/29/31	1	D in dilutions 1:10 to 1:20	0	..

TABLE 5.—*Serologic Tests for Syphilis, Case 5*

Date	Laboratory	Wassermann	Kahn Standard	Eagle Macro-flocculation	Eagle Micro-flocculation	Kline Diagnostic	Hinton	Kline Exclusion	Kahn Presumptive
10/14/38	1	..	P	..	..	..	..	..	..
10/20/38	1	..	P	..	..	..	..	..	..
10/24/38	2	P (66 units)	0	0	..	.	..	..	..
10/25/38	2	P (25 units)	0	0	..	..	..	..	..
	3	P (24 units)	0	..	0	0	0	..	..
	4	P (18 units)	..	..	0	..	..	..	..
10/28/38	2	P (25 units)	0	0	..	..	..	..	..
	5	0	..	..	..	0	..	..	..
11/ 1/38	6	D	D	..	..	..	0	..	..
	7	..	D	..	..	..	..	..	P
	8	..	..	..	..	0	..	0	..
11/ 8/38	5	0	..	..	..	0	..	..	..
3/30/39	2	0	0	0	..	..	..	..	..

antigens, the absence of a history of syphilis and indeed the probable lack of opportunity for acquiring it, the freedom from physical evidence of syphilis or of any other disease, all justify the classification of this patient as nonsyphilitic.

CASE 5.—A white man aged 25, an accountant, was found, on Oct. 14, 1938, because his employer demands yearly physical examinations, to have a positive serologic reaction for syphilis. He gave no history of syphilitic infection and had had only three sexual exposures—in June 1936, January 1938 and May 1938. Serologic tests for syphilis were negative in January 1938. There was nothing

in the history to suggest either acquired or congenital syphilis. He did have a head cold two days after the first positive serologic reaction, but this cold had disappeared before he was examined by us. The patient had no objective or subjective signs or symptoms of syphilis. There was no evidence of any other organic disease. All routine laboratory studies gave negative results. The reaction to a test for heterophil antibody was negative. A complement fixation test done with spirochetal antigen[15] gave a negative result. The serologic picture resembled that often observed in infectious mononucleosis inasmuch as the complement fixation test gave a strongly positive reaction (66 units) at a time when the results of flocculation tests were negative or doubtful, but there was no clinical or other laboratory evidence justifying such a diagnosis. A definite zone phenomenon was noted in the quantitative Wassermann test. The serologic tests for syphilis are summarized in table 5. The spontaneous reversal of the serologic result and the absence of any other evidence for syphilis or any other infectious disease justify the diagnosis of false positive reactions occurring in tests of a normal person.

Case 6.—A white man aged 26, an officer on a steamship, had had occasional attacks of pain in the lower right quadrant of the abdomen in the past two years.

Table 6.—*Serologic Tests for Syphilis, Case 6*

Date	Laboratory	Wassermann	Eagle	Kahn	Kline Diagnostic	Hinton	Kline Exclusion	Sigma
1/31/39	1	0	P	0	0	..	D	..
2/ 2/39	1	0	P	0	0	..	D	..
2/ 7/39	1	0	D	..	0	..	D	..
2/ 8/39	2	0	0	0	0	P	..	..
7/15/39	3	0	..	0	..	..	..	0

Because he was at sea for long periods, he was advised by the physician of the steamship company to have his appendix removed, even though he was symptomless at the time. An appendectomy was performed on Jan. 31, 1939, and a chronically inflamed appendix was removed. Before the operation routine serologic tests for syphilis were done and the results reported as doubtful. The patient had no subjective or objective signs or symptoms of syphilis or of any other disease. He had had only one sexual exposure in his life, two years previously. His mother and father are living and well; there is no history of lesions suggestive of congenital syphilis in his brothers or sisters. Routine laboratory studies gave negative results. The serologic tests for syphilis are summarized in table 6.

Case 7.—A white man, aged 32, a musician, consulted his physician on Feb. 2, 1940, because of "fluttering of his heart." The symptoms had been present only a few days. There was no history of precordial pain, dyspnea, cough or edema of the ankles. Two or three weeks before examination he complained of substernal oppression, which has since disappeared.

He gave no history of either acquired or congenital syphilis. The results of his mother's serologic tests for syphilis were negative. The patient stated that at one time he had a small abscess on the shaft of the penis, which was opened and

15. The antigen used was palligen, commercially available in Germany. Although the exact method of preparing the antigen has not been published, it is based on phenolizing cultures of the Reiter strain of S. pallida.

drained and which disappeared in two days. During the period of observation concerned here he had another such abscess in a hair follicle at the base of the penis. He had had slight albuminuria for thirteen years. His physical examination showed nothing abnormal. Routine laboratory examination gave normal results except for slight albuminuria. There was no disturbance of renal function. The cerebrospinal fluid was normal. The serologic tests for syphilis are summarized in table 7.

TABLE 7.—*Serolgoic Tests for Syphilis, Case 7*

Date	Laboratory	Wassermann	Eagle	Kahn Diagnostic	Kline Diagnostic	Hinton	Kahn Presumptive	Kline Exclusion
2/ 7/40	1	0	..	..	..	D	..	..
2/12/40	1	0	..	..	..	D	..	..
	2	D	..	0	..	..	..	..
2/26/40	1	D	..	..	..	D	..	..
	2	P	..	D	..	..	..	..
3/11/40	1	0	..	..	..	D	..	..
	2	P	..	0	..	..	..	..
3/25/40	3	0	..	0	..	..	..	..
4/10/40	4	P	P	..	..	..	..	..
	5	0	0	0	..	..	..	..
4/30/40	6	..	0	..	D	..	..	D
	7	0	0	0	0	..	..	..
	8	..	..	0	..	..	D	..

TABLE 8.—*Serologic Tests for Syphilis, Case 8*

Date	Laboratory	Complement Fixation	Eagle Macroflocculation	Eagle Microflocculation	Kahn Diagnostic	Kahn Presumptive	Kahn Verification	Kline Diagnostic	Kline Exclusion	Palligen
4/22/38	1	..	..	..	0	..	..	D	D	..
4/28/38	1	..	..	..	0	..	..	D	D	..
	2	A.C.	D	..	D	..	..	..	..	..
9/19/38	1	..	..	..	0	..	..	D	D	..
4/19/40	3	..	..	0	..	..	..	..	..	..
	1	..	..	..	0	..	..	D	P	..
4/30/40	4	..	..	..	..	..	..	D	D	..
	5	..	..	..	..	..	..	D	D	..
	1	..	..	0	..	..	..	D	D	..
5/ 2/40	2	0	0	..	0	..	..	..	..	..
5/ 9/40	3	0	..	0	D	..	..	P	..	..
	1	..	..	0	..	..	..	D	P	..
	4	..	..	..	..	..	..	D	D	..
	5	..	..	..	..	..	..	D	D	..
	6	..	..	..	..	..	..	..	..	0
	7	..	..	..	D	P	0	..	..	..
	2	0	0	..	0	..	..	..	..	..

CASE 8.—A white woman aged 55, a seamstress, consulted a physician two years ago (April 1938) because of swelling of the left middle finger and pain in the knee joints. At the time of this consultation serologic tests for syphilis were done and the results reported as doubtful. Within three months of this discovery the arthralgia spontaneously disappeared. Serologic tests were done on two occasions in 1938, with essentially similar results. In April 1940 she consulted her physician again for routine examination. He repeated the serologic tests and, confronted with

identical results, referred her to us. At this time (1940), she has no complaints and gives no history of either acquired or congenital syphilis. A physical examination has shown her to be in excellent health. The cerebrospinal fluid is normal.

The patient is married; her husband is well and his serologic reactions for syphilis are negative. She has two children living and well; serologic tests for syphilis were done in the case of one child and the results were negative.

Routine laboratory studies yielded negative information. The serologic tests for syphilis of this patient are summarized in table 8. No antisyphilitic treatment has been given at any time.

CASE 9.—A white man aged 26, an officer in the United States Navy, with no personal or familial history suggesting syphilis, applied for a marriage license in

TABLE 9.—*Serologic Tests for Syphilis, Case 9*

Date	Laboratory	Wassermann	Kahn Diagnostic	Kahn Presumptive	Kahn Verification	Kline Diagnostic	Kline Exclusion	Eagle Flocculation	Hinton	Palligen
8/19/39	1	..	..	..	..	0	..	0	..	..
8/—/39	2	..	D	..	..	..	..	..	..	..
9/—/39	2	..	P	P	..	..	..	..	..	..
	3	..	P	..	..	..	..	P	..	..
10/26/39	1	..	..	..	..	P	..	P	..	..
	4	0	D	..	..	..	..	..	..	..
	5	0	P	..	..	D	D	..	..	..
11/—/39	6	0	..	..	..	D	..	P	..	0
11/27/39	1	..	..	..	..	P	..	P	..	..
	4	0	D	..	..	..	D	..	..	..
	5	0	D	..	..	..	..	..	..	..
	7	0	..	..	..	..	..	..	..	..
1/30/40	3	..	P	..	..	..	..	P	..	..
2/19/40	3	Cerebrospinal fluid completely normal								
4/ 1/40	3	..	D	..	..	..	..	P	..	..
	5	0	P	..	..	D	D	P	..	..
	8	0	..	..	..	..	..	D	..	..
6/ 5/40	9	0	P	..	..	..	..	D	..	..
	2	..	0	D	0	..	..	..	..	..
	10	0	0	..	..	..	..	..	D	..
	11	..	..	..	..	D	D	D	..	..
	6	..	..	..	..	..	..	..	..	0
6/16/40	9	0	D	..	..	..	..	D	..	..
	12	0	0	..	..	0	0	0	..	..
	6	..	..	..	..	..	..	..	..	0

Michigan in August 1939. The serologic tests required by law were performed in another state (laboratory A) and the results were reported negative. Since this laboratory was not approved by the Michigan State Department of Health, other tests were required from a Michigan laboratory (B); those done about one week after the first tests gave doubtful results, and those done one week later still (in two laboratories, B and C) gave positive reactions. These results caused the refusal of a marriage license and initiated a long and extensive investigation for syphilis, which has now lasted for ten months and has caused two hospital admissions, two separate examinations of the cerebrospinal fluid (both showing the fluid to be normal) and laboratory studies in twelve different laboratories by nine different technics on eleven different samples of blood. These tests are summarized in table 9.

From the anamnestic standpoint, not only is a history of syphilis lacking, but there has been only one sexual exposure, with a social equal, in the summer of 1936. The original positive serologic reactions in August 1939 were not preceded

by any recognizable acute infection. His physical status, as determined by several observers over the ten month period of investigation, has always been normal, and there are no abnormalities suggesting syphilis.

The serologic picture is somewhat beclouded by the facts that (1) on Oct. 27 and Nov. 1, 1939 two injections each of neoarsphenamine (0.35 and 0.4 Gm) and of bismuth subsalicylate (each 0.2 Gm.) were given (but there was no effect from this on subsequent serologic tests) and (2) no quantitative titrations were performed. By the time the patient reached our hands, in June 1940, the quantity of reacting substance in his blood was too small for quantitation.

All other laboratory studies in June 1940, including examination of blood smears for malaria and infectious mononucleosis, examination of serum for heterophil antibody and determination of the sedimentation rate, gave negative results.

From the purely serologic standpoint it is to be noted that (1) the quantity of reacting substance in the blood has always been small (many doubtful results interspersed with the positive), (2) the supersensitive Kline exclusion test has always given a doubtful result when less sensitive tests showed positive results, (3) the complement fixation test with spirochetal antigen has given negative results on three occasions over an eight month period and (4) the Kahn "verification test" has given a negative result.

The conclusion is inescapable that this patient is a normal nonsyphilitic person with biologic false positive serologic reactions.[16]

COMMENT

We have reported 9 examples of what we regard as biologic false positive reactions to serologic tests in normal, nonsyphilitic persons. It is only fair to say that various readers may not agree with our interpretation. Indeed, before our own doubts arose as to the almost absolute specificity of serologic tests, we ourselves would have regarded some or all of these patients as having latent syphilis.

The demonstration by three different groups of workers (Malloy and Kahn; Barnett, Jones and Kulchar; Sherwood, Bond and Canuteson) that some normal human serums may contain reagin or reagin-like factors is of obvious significance for the practical serologic diagnosis of syphilis. It is true that the amount of reactive material which these workers have been able to demonstrate is well below the threshold concentration which can be detected by the standard diagnostic procedures. Under ordinary circumstances the reactivity of normal serum therefore does not complicate the diagnostic test. The 9 cases here presented, nevertheless, indicate that in the exceptional case this normal factor may be present in sufficient concentration to give biologic false reactions.

Despite these false reactions, it may be that the antibody present in syphilitic serum is strictly specific and that normal serum contains other substances with qualitatively similar effects on the lipoidal suspensions used as "antigen." Thus, a normal serum may be capable of causing the aggregation of these lipoidal suspensions to give clumps indistinguishable

16. Further tests on this patient have continued to show wholly negative results as late as Oct. 1, 1941.

from those caused by syphilitic serum, despite the fact that the mechanism of the aggregation may be altogether dissimilar. We shall discuss in a later paper ways and means which are now available to differentiate nonspecific reactions from those actually due to syphilitic infection.

CONCLUSIONS

We have reviewed the literature on the presence of a reagin-like substance in normal serum and have briefly described 9 cases in which we believe the serums of normal persons gave biologic false positive reactions for syphilis.

PROGNOSTIC VALUE OF VARIOUS CLINICAL AND ELECTROCARDIOGRAPHIC FEATURES OF ACUTE MYOCARDIAL INFARCTION

I. IMMEDIATE PROGNOSIS

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Within the past thirty years myocardial infarction has risen from the position of a purely pathologic entity to the ranks of those diseases which are of first importance to the clinician. Those observers who were responsible for this rise include Dock,[1] Obrastzow and Straschesko,[2] Hochhaus[3] and Herrick,[4] all of whom were instrumental in first calling attention to the clinical picture of the disease. They were soon followed by a large group of others[5] who made many valuable contributions. Beginning with the work of Smith[6] and Pardee,[7] a great number of electrocardiographic studies[8] not only provided a means of

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1. Dock, G.: Notes on the Coronary Arteries, Ann Arbor, Mich., The Inland Press, 1896.

2. Obrastzow, W. P., and Straschesko, N. D.: Zur Kenntnis der Thrombose der Koronararterien des Herzens, Ztschr. f. klin. Med. **71**:116, 1910.

3. Hochhaus, H.: Zur Diagnose des plötzlichen Verschlusses der Kranzarterien des Herzens, Deutsche med. Wchnschr. **37**:2065, 1911.

4. Herrick, J. B.: Clinical Features of Sudden Obstruction of the Coronary Arteries, J. A. M. A. **59**:2015 (Dec. 7) 1912.

5. (*a*) Levine, S. A., and Tranter, C. L.: Infarction of the Heart Simulating Acute Surgical Abdominal Conditions, Am. J. M. Sc. **155**:57 (Jan.) 1918. (*b*) Wearn, J. T.: Thrombosis of the Coronary Arteries with Infarction of the Heart, ibid. **165**:250 (Feb.) 1923. (*c*) Gardinier, H. C.: Coronary Arterial Occlusion: A Perfectly Definite Symptom Complex, ibid. **168**:181 (Aug.) 1924. (*d*) Hamman, L.: The Symptoms of Coronary Occlusion, Bull. Johns Hopkins Hosp. **38**:273 (April) 1926.

6. Smith, F. M.: The Ligation of Coronary Arteries with Electrocardiographic Study, Arch. Int. Med. **22**:8 (July) 1918.

7. Pardee, H. E. B.: Heart Disease and Abnormal Electrocardiograms, with Special Reference to the Coronary T Wave, Am. J. M. Sc. **169**:270 (Feb.) 1925.

8. (*a*) Robinson, G. C., and Herrmann, G.: Paroxysmal Tachycardia of Ventricular Origin and Its Relation to Coronary Occlusion, Heart **8**:59 (Feb.) 1921.

(Footnote continued on next page)

confirming the diagnosis but made it possible to localize the area of necrosis in the heart muscle with a high degree of accuracy. As a result of these advances myocardial infarction has become "an easily diagnosable disease" (Christian [9]). In spite of this progress in knowledge of the condition, prognosis in cases of myocardial infarction remains uncertain. As Levine [10] has put it, "there are few diseases in which the prognosis in any individual case is more difficult to predict than in coronary thrombosis." Levy [11] concurred in this opinion, while Glendy, Levine and White [12] have indicated that it holds true as well for coronary disease in early life.

The general immediate mortality of an attack of myocardial infarction at first was thought to be about 50 per cent. In later publications this figure was reduced to 24 per cent,[13] and even 8 per cent.[14] This decrease in the immediate mortality was due not so much to any improvement in the manner of treatment but rather to a greater accuracy in diagnosis. As a result, many cases of mild infarction were discerned that formerly would not have been recognized or would have been regarded as questionable. So far, the physician has had little to guide him in predicting the immediate outcome in any specific case. It is our purpose here to review in detail the cases of a large number of patients suffering from their first attack of myocardial infarction in order to determine whether there are any clinical or electrocardiographic features which will lead to more accurate prognosis in individual cases.

(*b*) Willius, F. A., and Barnes, A. R.: Myocardial Infarction: An Electrocardiographic Study, J. Lab. & Clin. Med. **10**:427 (March) 1925. (*c*) Rothschild, M. A.; Mann, H., and Oppenheim, B. S.: Successive Changes in the Electrocardiogram Following Acute Coronary Artery Occlusion, Proc. Soc. Exper. Biol. & Med. **23**:253 (Jan.) 1926. (*d*) Wilson, F. N.; Macleod, A. G.; Barker, P. S.; Johnston, F. D., and Klostermeyer, L. L.: The Electrocardiogram in Myocardial Infarction with Particular Reference to the Initial Deflections of the Ventricular Complex, Heart **16**:155 (June) 1933. (*e*) Barnes, A. R.: Electrocardiographic Patterns: Their Diagnostic and Clinical Significance, Springfield, Ill., Charles C. Thomas, Publisher, 1940.

9. Christian, H. A.: Coronary Thrombosis: An Easily Diagnosable Disease, Am. Heart J. **1**:129 (Dec.) 1925.

10. Levine, S. A.: Coronary Thrombosis: Its Various Clinical Features, Baltimore, Williams & Wilkins Company, 1929.

11. Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, The Macmillan Company, 1936, chap. 8.

12. Glendy, R. E.; Levine, S. A., and White, P. D.: Coronary Disease in Youth: A Comparison of One Hundred Patients Under Forty with Three Hundred Persons Past Eighty, J. A. M. A. **109**:1775 (Nov. 27) 1937.

13. Howard, T.: Coronary Occlusion, Based on the Study of One Hundred and Sixty-Five Cases, M. Times & Long Island M. J. **62**:337 (Nov.) 1934.

14. Master, A. M.; Jaffe, H. L., and Dack, S.: The Treatment and Immediate Prognosis of Coronary Artery Thrombosis, Am. Heart J. **12**:549 (Nov.) 1936.

MATERIAL AND METHOD

In this portion of the study (part I) a review was made of the cases of all patients entering the Peter Bent Brigham Hospital between December 1935 and June 1940 whose diagnosis at discharge included myocardial infarction. From these patients were selected, in consecutive fashion, all those whom we believed to be suffering from their first attack. We have thus avoided the confusion in both the clinical and the electrocardiographic picture which so often arises when one is dealing with patients who have suffered multiple attacks. Only those patients were included for whom the diagnosis was felt to be definite. A large percentage of the patients were seen by one or both of us. Each case record was analyzed in detail, and the electrocardiograms were reviewed. On the basis of the electrocardiograms the entire series of patients was divided into six groups distinguished by the presence of (1) anterior infarction, (2) posterior infarction, (3) bundle branch block, (4) partial or complete block, (5) defective intraventricular conduction or (6) low voltage of the QRS complex in the standard three leads. A seventh, unclassified group included patients for whom the changes were not distinctive but the diagnosis was certain from clinical evidence alone. In addition, 1 patient with infarction of the right anterior ventricular wall was included in the series. That we were dealing with patients in whom infarction was recent was indicated by the fact that 82 per cent of them had electrocardiograms within the first five days of the time of onset of symptoms. Under the term immediate mortality we included death within one month after the onset of the attack, either from the infarction or from its complications.

In analyzing the prognostic significance of the various clinical features, such as pain, dyspnea, cyanosis and shock, we appraised their presence and development throughout the early hours and days of the disease. It obviously would be futile to regard in the same light a patient who showed shock or dyspnea only an hour or so before he died after having been free from these symptoms for a week and one who manifested similar features at the onset of the attack. In this way an attempt was made to find out the prognostic value of various aspects of the clinical symptoms of coronary thrombosis as they present themselves in general practice.

NUMBER OF PATIENTS AND MORTALITY

In the four and one-half year period covered by this study there were 208 patients whose cases fitted the limitations set forth in the preceding sections. Those patients who died as a result of this first attack or its complications totaled 68, or 33 per cent. This is a figure which we recognize as being definitely higher than the 8 per cent of Master, Jaffe and Dack,[14] the 16.2 per cent found by Conner and Holt [15] or the 24 per cent cited by Howard.[13] However, all our patients were sick enough to require admission to a hospital, and thus the series does not include those with a milder form of illness who did not come to a physician until after they had recovered or who could be cared for at home. Moreover, the mortality in this series is definitely lower than in those reported by Levine (53 per cent),[10] Clark (48 per cent) [16]

15. Conner, L. A., and Holt, E.: The Subsequent Course and Prognosis in Coronary Thrombosis, Am. Heart J. **5**:705 (Aug.) 1930.

16. Clark, L. J.: Prognosis in Coronary Disease, New Orleans M. & S. J. **86**:365 (Dec.) 1933.

and Cooksey (39.6 per cent),[17] in which patients suffering initial and recurrent attacks were not separated. This is in agreement with the general feeling of most observers [18] that the possibility of a fatal outcome increases with each attack.

ELECTROCARDIOGRAPHIC OBSERVATIONS

Dividing the entire series into groups depending on the electrocardiographic changes yielded the following information (table 1): Anterior infarction was present in 109 patients, or slightly over one half of the total; patients with a lesion in this location had a mortality of 30 per cent. Those with posterior infarction totaled 64, with a mortality of 36 per cent, slightly higher than that in the former group. For some time there has been disagreement in the literature regarding this point, and it was this very question which initiated the present study.

TABLE 1.—*Distribution of Two Hundred and Eight Patients with Initial Acute Myocardial Infarction According to Electrocardiograms*

Group	Number of Patients	Number of Deaths	Mortality, Percentage
Anterior infarction	109	33	30.0
Posterior infarction	64	23	36.0
Bundle branch block	9	7	78.0
Partial and/or complete heart block	7	3	43.0
Low voltage of QRS complex in standard leads	3	0	0.0
Defective intraventricular conduction	3	0	0.0
Unclassified	12	1	8.0
Right ventricular infarction *	1	1	100.0
Total	208	68	32.7

* Localization in the case of this patient was made at a postmortem examination.

Vander Veer and Brown,[19] Stroud [20] and Wood and associates [21] have expressed the belief that anterior myocardial infarction is far more serious than one involving the posterior wall of the left ventricle. Our results tend to confirm the conclusion of Master and co-workers [14] and of Willius [18] that the mortality in the two groups is practically identical.

17. Cooksey, W. B.: Coronary Thrombosis: Follow-Up Studies with Especial Reference to Prognosis, J. A. M. A. **104**:2063 (June 8) 1935.

18. Willius, F. A.: Life Expectancy in Coronary Thrombosis, J. A. M. A. **106**:1890 (May 30) 1936.

19. Vander Veer, J. B., and Brown, L. E.: The Diagnosis and Prognosis of Coronary Occlusion: The Electrocardiogram as an Aid, Pennsylvania M. J. **39**: 303 (Feb.) 1936.

20. Stroud, W. D., in discussion on Levine, S. A., and Levine, H. D.: Electrocardiographic Study of Lead IV with Special Reference to Findings in Angina Pectoris, Tr. A. Am. Physicians **50**:303, 1935.

21. Wood, F. C.; Bellet, S.; McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion: Further Observation on the Use of Chest Leads, Arch. Int. Med. **52**:752 (Nov.) 1933.

From our data it would appear, however, that anterior infarcts are somewhat more frequent than posterior lesions in initial attacks. Here, again, our method of selection may account for the apparent disagreement with the conclusion of Barnes and Ball,[22] who dealt with unselected autopsy material, and of Master and associates [14] that the frequency of infarction of the two locations is apparently equal.

The smaller groups based on other electrocardiographic changes make up the remainder of the entire series. Bundle branch block occurred in 9 patients, with a mortality of 78 per cent. Master and co-workers [23] found a similar higher mortality among patients with such a lesion as compared with the mortality among those with normal intraventricular conduction. There were 7 instances of partial or complete heart block or both, in 43 per cent of which the outcome was fatal. Low voltage of the ventricular complexes with no other changes and defective intraventricular conduction with no accompanying alterations each appeared 3 times, with no fatalities. Twelve patients fell into the unclassified group, with a single death for a mortality of 8 per cent. Among them were included those whose electrocardiograms showed no significant changes or only minor abnormalities that could not be helpful in diagnosis. It is interesting that 1 such patient died of a rupture of the area of infarction on the third day, and yet no significant abnormalities of the ventricular complex had been shown in two tracings taken on the first and on the third day. Although these groups are small, it would appear that in general those patients with less striking electrocardiographic changes have a distinctly better outlook, for there was only 1 death among 18 patients in groups 5, 6 and 7 (table 1). In our single case of right ventricular infarction the diagnosis was made at autopsy.

Throughout this study, in analysis of the different clinical features, the influence of various electrocardiographic changes, especially those which differentiate anterior and posterior infarctions, was evaluated. There was one other alteration in the electrocardiogram which we thought worth while to investigate, i. e., the low voltage of the QRS complex in the standard three leads. Wearn [5b] was among the first to call attention to this alteration in cases of acute coronary thrombosis. Barnes [24] reported that this change was encountered twice as often in

22. Barnes, A. R., and Ball, R. G.: The Incidence and Situation of Myocardial Infarction in One Thousand Consecutive Postmortem Examinations, Am. J. M. Sc. **183**:215 (Feb.) 1932.

23. Master, A. M.; Dack, S., and Jaffe, H. L.: Bundle Branch Block and Intraventricular Block in Acute Coronary Artery Occlusion, Am. Heart J. **16**: 283 (Sept.) 1938.

24. Barnes, A. R.: Electrocardiogram in Myocardial Infarction: A Review of One Hundred and Seven Clinical Cases and One Hundred and Eight Cases Proved at Necropsy, Arch. Int. Med. **55**:457 (March) 1935.

patients who died of coronary occlusion as it was in those who recovered and that its presence rendered the prognosis more grave. In our analysis, dealing solely with patients having their initial myocardial infarction, this was not the case. In the entire series, this change in the electrocardiogram was present in 26 per cent of all patients. It was much more common in those who had had no previous hypertension. Of the 54 patients who had a low voltage, 22 per cent died, as compared with a mortality of 35 per cent in 150 patients whose electrocardiograms did not show this change. It would thus appear that the presence of a low voltage of the QRS complex in the electrocardiograms of patients undergoing their first episode of acute coronary thrombosis tends to make the outlook somewhat more favorable.

SEX

Of the entire series of 208 patients, 69 per cent (143) were male and 31 per cent (65) were female. This ratio, with the obvious male predominance, is in accord with that in most large series of patients with coronary occlusion.[25] The higher percentage of men was somewhat more striking in the group with posterior infarction (78 per cent) and in the smaller group with partial and complete block (86 per cent). On the other hand, the mortality for all men was 31 per cent, as compared with 35 per cent for all the women. This disparity in male and female mortality rates was almost equally evident in the case of anterior and of posterior infarction. The trend toward a graver prognosis for women may well be accounted for by two factors, which will be discussed later: 1. The average age of women at the time of their first attack tends to be higher. 2. A greater number of women have a history of hypertension antedating the occurrence of myocardial infarction.

AGE

The average age for the entire series was 58.7 years. For the men the average was 57.4 years, while for the women it was 61.5 years. These findings are in accord with previous reports.[26] It was observed that 70.5 per cent of all patients fell into the age period between 50 and 69. However, the largest percentage of men in any single decade was 38 per cent, in the 50 to 59 year age period. Women, on the other hand, showed a definite predominance in the 60 to 69 year age period, into which 47 per cent of all patients fell. The fact that a greater proportion of women with coronary occlusion fall into the later period has been observed by Willius [18] and by Conner and Holt.[15] Here it is seen to hold true, even when one is dealing solely with patients having their first attack.

25. Levine.[10] Master, Jaffe and Dack.[14] Conner and Holt.[15] Willius.[18]
26. Levine.[10] Master, Jaffe and Dack.[14] Conner and Holt.[15]

The average age of those patients that died was 60.8 years, which was definitely higher than that of those who lived, 57.6 years. This difference was true for patients of both sexes. The average age of the men who died was 59.6 years, as contrasted with 56.3 years for those who lived. The average for the women who died was 63.3 years, while for those who survived it was 60.6 years. Even more significant was the fact that the mortality in each decade rose progressively as the older decades were reached, with the exception of that of 30 to 39 years, in which the total number of patients was too small to be evaluated. Thus the patients in the decades from 40 to 49 and 50 to 59 had a mortality of 25 per cent, while 36 per cent of those from 60 to 69 and 50 per cent of those from 70 to 89 died. Previous authors [27] have also noted that the younger patients withstand cardiac infarction better than do the older ones.

It is noteworthy that the average ages of the patients in the groups with anterior and with posterior infarction were nearly identical. The distribution over the various decades was alike in the two groups, there being the same proportion of anterior to posterior lesions in those patients under 59 years as in those over 59. The greater age of the women and the higher mortality in the older age ranges were noted equally in the two groups. The foregoing generalizations were true as well in the smaller groups of patients showing other electrocardiographic patterns.

We may conclude that, in general, women are 4 years older than men at the time of the initial acute attack, that for both sexes the mortality increases with advancing years and that these statements are true whether the infarction be anterior or posterior.

PREVIOUS ANGINA PECTORIS

It has long been known that angina pectoris often precedes myocardial infarction.[28] In this series, antecedent angina pectoris or its equivalent was present in 71.6 per cent of all patients. It was equally common in men and in women. It was noted just as frequently in patients who had anterior infarction as in those who had posterior infarction. It was found somewhat more often in those with bundle

27. (*a*) King, H. C.: Prognosis in Coronary Heart Disease and After Coronary Occlusion, Ohio State M. J. **33**:524 (May) 1937. (*b*) Master, Jaffe and Dack.[14] (*c*) Conner and Holt.[15] (*d*) Cooksey.[17]

28. (*a*) Parkinson, J., and Bedford, D. E.: Cardiac Infarction and Coronary Thrombosis, Lancet **1**:4 (Jan. 7) 1928. (*b*) Smith, F. M.; Rathe, H. W., and Paul, W. D.: Observations on the Clinical Course of Coronary Artery Disease, J. A. M. A. **105**:2 (July 6) 1935. (*c*) Levine.[10] (*d*) Howard.[13] (*e*) Conner and Holt.[15] (*f*) Willius.[18]

branch block or with defective intraventricular conduction. It tended to be more frequent in our series than in those previously reported, but this may well be explained by the fact that our patients were hospitalized and thus it was possible to obtain a more detailed and exhaustive history. White [29] and Bedford [30] found that the previous existence of angina pectoris or its duration prior to the attack had no influence on the prognosis of coronary thrombosis. The striking feature here is that the mortality of those patients with previous angina pectoris was only 29 per cent, as contrasted with that of 38 per cent for all patients without antecedent pain. Here, again, the differences were the same in the groups with anterior and with posterior lesions. This would seem to indicate that those patients with previous angina pectoris actually do a little better and that there is possibly some truth in the old clinical impression that those without antecedent pain are caught unprepared with less adequate collateral circulation and succumb more easily.

PREVIOUS HYPERTENSION

Reports in the literature regarding the frequency of hypertension antedating coronary occlusion are not entirely in agreement. Master and co-workers [14] found preexisting hypertension in 66 per cent of their series. It was present in 34 per cent of Conner and Holt's [15] series. Howard [13] observed it in 28 per cent of his cases. There were 58 hypertensive patients in Levine's [10] series of 145, though information on previous blood pressures was not entirely complete. In our series we have used the criterion of 150 mm. of mercury systolic and (or) 100 mm. of mercury diastolic. The blood pressure readings used under this criterion were those observed or reported prior to the attack in many instances; in others the blood pressure on admission was used, if it was still high and if the patient entered the hospital within a short time after the onset. If the data were inadequate, the case was not included in this analysis. Hypertension existing before the first attack of coronary thrombosis was recorded in 57 per cent of 197 patients for whom pressure readings were known. Interestingly enough, it was far more common in women (86 per cent) than in men (44 per cent). Previous hypertension was equally common in the group with anterior and in that with posterior infarction. Although they form only a small group, it is worthy to note that all the patients with bundle branch block had previous hypertension, a finding similar to one previously reported.[28]

29. White, P. D.: The Prognosis of Angina Pectoris and Coronary Thrombosis, J. A. M. A. **87**:1525 (Nov. 6) 1926.

30. Bedford, D. E.: Prognosis in Coronary Thrombosis, Lancet **1**:223 (Jan. 26) 1935.

It was the impression of Vander Veer and Brown [19] and Bedford [20] that the mortality is no higher in the group with hypertension than in the group without, although Master and associates [31] found a higher mortality in those with previous hypertension. Our findings are in accord with the latter observation. The mortality for those patients with previous hypertension was 36 per cent, as contrasted with a rate of 24 per cent for those with a previously normal blood pressure.

An interesting side light which developed in this analysis, and which is in agreement with the observations of Eppinger and Levine,[32] was that of 59 women for whom adequate data were available, only 2 (3.4 per cent) had had neither angina pectoris nor hypertension before the initial attack of coronary thrombosis. On the other hand, of 137 men, 25 (18.2 per cent) had had neither prior to their cardiac infarction. As a corollary of these observations regarding both previous angina pectoris and previous hypertension, it was seen that of patients with the four possible combinations of these two characteristics, those who did the poorest were the patients who had been hypertensive but had had no cardiac pain.

From the foregoing statements it follows that previous hypertension occurs in slightly more than the majority of patients, that hypertension is much more common in women and that the immediate mortality is distinctly greater among hypertensive patients. The combination of absence of antecedent angina and absence of hypertension is extremely rare in women. Finally, the presence of previous hypertension without previous angina is associated with a particularly high mortality. These generalizations were valid whether the infarct was located anteriorly or posteriorly.

BLOOD PRESSURE

A fall in the blood pressure is such a common concomitant of acute myocardial infarction that it has become one of the observations sought for most frequently at the bedside when the diagnosis of such a condition is suspected. In our series there were 170 patients for whom the data regarding changes in blood pressure were felt to be adequate. Here, again, as in the analysis of other features in this investigation, the changes in pressure during the early hours or days were studied, exclusive of the terminal fall in pressure that obviously occurs in most cases of fatal termination.

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31. Master, A. M.; Dack, S., and Jaffe, H. L.: Coronary Thrombosis: An Investigation of Heart Failure and Other Factors in Its Course and Prognosis, Am. Heart J. **13**:330 (March) 1937.

32. Eppinger, E. C., and Levine, S. A.: Angina Pectoris: Some Considerations with Special Reference to Prognosis, Arch. Int. Med. **53**:120 (Jan.) 1934.

In the group of 170 patients, an appreciable drop (20 mm. of mercury or more) in systolic pressure occurred in 68 per cent, while in 32 per cent there was no appreciable fall (less than 20 mm. of mercury). The former group was made up of 88 patients who had previous hypertension and 27 who had previous normal pressure. With 1 exception, all those whose pressure showed no significant fall had previous normal pressures. The mortality among those patients showing a definite fall in blood pressure was somewhat higher (30 per cent) than among those who did not demonstrate such a change (24 per cent).

On a closer analysis of cases in which there was an appreciable fall in systolic pressure, it was observed that in patients who had previous hypertension, the average greatest fall in pressure was somewhat higher among those who died (71 mm. of mercury) than among those who recovered (59 mm. of mercury). In those with previous normal pressures, the average fall in the systolic level appeared to be the same (about 38 mm. of mercury) whether the patient died or recovered. It was noted, however, that many patients with previous hypertension were able to tolerate a drop in systolic pressure as great as 75 to 110 mm. whereas others who died showed a fall of much less extent. It would appear, therefore, that the actual degree of fall in systolic pressure is not of great prognostic significance. However, it was our distinct impression that when the pressure was maintained at a level below 80 mm. systolic for many hours or days the outlook became unfavorable. A similar belief was expressed by Middleton[33] and by Bedford.[30]

A study was also based on the lowest pulse pressure observed during the course of the patient's illness. Master and his co-workers[31] reported a mortality of 58 per cent in patients with pulse pressures of 20 mm. or less, as compared with 14 per cent in those with pulse pressures of 30 mm. or more. In our series, the result has been much the same, there being a mortality of 54 per cent in those whose lowest pulse pressure was less than 20 mm. and of 30 per cent in all those whose lowest pulse pressure was above that level. This fact was true regardless of the electrocardiographic pattern.

Wood and associates[21] noted that in some cases of acute coronary thrombosis the blood pressure did not begin to drop until twelve hours after the initial symptoms appeared. Fishberg and his co-workers[34] noted that in some cases the blood pressure may actually rise for a time. They expressed the belief that this occurred when failure of the

33. Middleton, W. S.: The Prognosis and Treatment of Coronary Occlusion, Minnesota Med. **18**:710 (Nov.) 1935.

34. Fishberg, A. M.; Hitzig, W. M., and King, T. H.: Circulatory Dynamics in Myocardial Infarction, Arch. Int. Med. **54**:997 (Dec.) 1934.

left ventricle was severe enough to produce outspoken pulmonary edema and that it was largely a consequence of asphyxia. In this series there were 10 patients for whom the data available were complete enough for it to be said with certainty that a rise in the blood pressure level accompanied the onset of myocardial infarction, the customary fall then occurring after some hours or days. Three of these patients had had previous hypertension, while in the others the previous levels had been normal. In the majority the rise in blood pressure was observed while the patient was suffering from pain, but this was not always the case. In 2 patients, 1 of whom was previously hypertensive, the highest blood pressure level was observed three days after the onset of symptoms. In only 1 case was this phenomenon associated with acute pulmonary edema. Four patients had anterior infarcts, 3 had a posterior lesion, 1 had defective intraventricular conduction and the remaining 2 fell into the unclassified group. It is also worth while to note that all of these patients recovered. The mechanism of this temporary rise in blood pressure is not clear. In a study of patients with angina pectoris, Levine and Ernstene [35] concluded that pain alone as a stimulus was not sufficient to cause the elevation of blood pressure during attacks of cardiac pain. Whatever the explanation for this phenomenon may be, it is well to remember that it can occur, and the diagnosis should not be ruled out because of an initial rise or a failure of the blood pressure to fall during the first few hours or days following acute myocardial infarction.

PAIN

Pain is perhaps the symptom most commonly found in patients with myocardial infarction. It is well recognized that its severity and location vary greatly from patient to patient. It seemed worth while to analyze this feature in detail to determine any prognostic significance it might have. In order to do this the pain, as experienced by each patient, was classified as absent, mild, moderate or severe, depending on its intensity and duration. Again the cases were grouped, as in each analysis in this study, according to the electrocardiographic findings.

Previous observers [36] have expressed the belief that the severity of the pain during the attack had little influence on the outcome. Middleton [33] has found that some of the most ominous attacks are either mild or free from pain. On the whole, the results of our studies are in agreement with this point of view. There was no constant relation between the intensity of the pain and the prognosis, as was demon-

35. Levine, S. A., and Ernstene, A. C.: Observations on Arterial Blood Pressure During Attacks of Angina Pectoris, Am. Heart J. 8:323 (Feb.) 1933.

36. Willius.[18] Bedford.[30]

strated by the fact that of 46 patients with pain of mild degree 39 per cent died, of 110 patients with moderately severe pain 24 per cent died and of 47 with severe pain 43 per cent died. This conclusion is further borne out by the evidence that of 6 patients with no pain at all 5 died. Moreover, the average degree of pain for each of the various groups was nearly the same. The only exception to this was that patients with posterior infarction tended to have slightly less severe pain than those with anterior infarction.

The literature contains occasional comments [21] regarding the distribution of the pain as a guide to the location of the infarction. In this series 93 per cent of all patients had pain or similar feelings of distress, like constriction, burning or pressure, in some area of the chest; in 19 per cent there was radiation to the right arm (in all but 1 case there was also radiation to the left arm); in 48 per cent there was radiation to the left arm; in 14 per cent the discomfort was partially or wholly in the upper part of the abdomen, and in 16 per cent the distress radiated to the back. In one third of the patients the pain was experienced solely in the chest; 1, and possibly a second, patient had discomfort only in the left arm and shoulder, and in 5 patients the pain was entirely abdominal. None of the patients experienced distress solely in the right arm or in the back. Only 1 patient had thoracic pain with radiation to the right arm alone, whereas 47 patients (23 per cent) had thoracic pain with radiation to the left arm alone. Some patients with bilateral radiation had more marked discomfort in the right arm. For the most part, the site and the distribution of the pain appeared to play no role in the outcome, nor was there any definite relation to the electrocardiographic findings. Notable exceptions were as follows: First, patients with no thoracic pain at all had a higher mortality than those with such pain (11 deaths among 15 patients, i. e., 73 per cent, as compared with 56 deaths among 191 patients, i. e., 29 per cent). Second, patients with anterior infarction and pain radiating to the left arm did better than those with a lesion in the same location but without such distribution of pain (11 deaths among 55 patients, i. e., 20 per cent, as compared with 22 deaths among 54 patients, i. e., 41 per cent). Last, radiation of pain to the right arm was somewhat more frequent in patients with posterior infarction than in those with anterior infarction (17 of 64 patients, i. e., 22 per cent, as compared with 17 of 109 patients, i. e., 16 per cent).

As Levine and Tranter [5a] first pointed out in 1918, in some patients with coronary thrombosis the pain is localized wholly to the upper part of the abdomen. Five patients in our series fell into this category. Of this number, there were 3 with anterior infarction, all of whom died, the diagnosis being confirmed by postmortem examination in the 1

instance in which autopsy was permitted. There were 1 patient with a posterior infarct and 1 in the unclassified group; both these patients survived.

Of the entire group of 208 patients, there were 4 who had no pain or sense of oppression at all and 2 more in whom pain was thought to be absent but whose history was not satisfactory. Thus, at most, 3 per cent of the patients had "painless myocardial infarction." This finding corroborates those of Pollard and Harvill [37] and Kennedy,[38] although it is a far smaller percentage than that reported by Gorham and Martin.[39] Of these 6 patients, 4 had an anterior and 2 a posterior infarct. All of the former and 1 of the latter succumbed, the diagnosis and the location of the lesion being confirmed at autopsy in all cases.

We may summarize by stating that the severity and distribution of the pain were of little value in estimating the prognosis or in predicting the location of the infarction. It was also found that "painless" infarction is rare (3 per cent), that localization of pain of the upper part of the abdomen is also rare (2.4 per cent) and that although the numbers of patients with either condition may be small, the mortality may possibly be higher than the average.

DYSPNEA

As most clinicians are well aware, dyspnea may play a prominent role in the symptomatology of myocardial infarction. Perhaps because it is a more disagreeable sensation, the patient's attention is usually directed toward his pain. If he is questioned and observed closely, however, shortness of breath of varying degrees will be found in the majority of instances. In some cases extreme dyspnea may be the only complaint. Furthermore, as Christian [9] and Levine [10] have pointed out, there is frequently a disproportion between the degree of dyspnea and any abnormalities demonstrable in the heart or lungs. Bedford [30] has indicated that severe dyspnea is an unfavorable sign in coronary thrombosis.

In order to determine the value of this complaint as a prognostic indication the intensity of dyspnea presented by each patient was classified as absent, mild, moderate or severe. From this analysis it was learned that the patients who survived had definitely less dyspnea than those

37. Pollard, H. M., and Harvill, T. H.: Painless Myocardial Infarction, Am. J. M. Sc. **199**:628 (May) 1940.

38. Kennedy, J. A.: The Incidence of Myocardial Infarction Without Pain in Two Hundred Autopsied Cases, Am. Heart J. **14**:703 (Dec.) 1937.

39. Gorham, L. W., and Martin, S. J.: Coronary Artery Occlusion With and Without Pain: An Analysis of One Hundred Autopsied Cases with Reference to the Tension Factor in Cardiac Pain, Tr. A. Am. Physicians **53**:129, 1938.

who died. Furthermore, the average degree of dyspnea in patients with anterior and that in patients with posterior infarction were almost identical. Patients with bundle branch block had slightly more dyspnea, on the whole, than did those in other electrocardiographic groups, a feature which corresponds with the higher mortality among those with this type of lesion.

In summary, it was seen that in 29 per cent of the patients dyspnea was absent, in 24 per cent it was mild, in 28 per cent it was moderate and in 19 per cent it was severe. In a consideration of mortality, it was found that of 140 patients who recovered there were 63 per cent with no or mild dyspnea and 37 per cent with moderate or severe dyspnea whereas the corresponding figures for 68 patients who died were 34 and 66 per cent, respectively. This relation is further emphasized by the relative mortality for the four degrees of dyspnea (table 2). It was also noted that each of the 6 patients with myocardial infarction without pain had either moderate or severe dyspnea. Therefore this

TABLE 2.—*Significance of Dyspnea in Two Hundred and Eight Patients with Acute Myocardial Infarction*

Degree of Dyspnea	Number of Patients	Number of Deaths	Mortality, Percentage
Absent	61	11	18
Mild	50	12	24
Moderate	58	21	36
Severe	39	24	62

feature can serve not only as a key to prognosis but, in some cases, as an aid in diagnosis. It would appear, then, that the degree of dyspnea is a far more reliable indication of the patient's outlook than is the severity of pain.

SWEATING

In many cases patients who suffer from acute coronary occlusion will state that at the onset they "broke out in a cold sweat." In others, the skin on first examination will be found to be excessively moist. In fact, some patients will have a moist skin for many days or weeks after the onset. The frequent occurrence of sweating is indicated by the fact that it was present in 70 per cent of the patients. It was seen slightly more often in those who died, but the very fact that it is so common lessens its prognostic importance. It is our impression, however, that a patient should be given a more guarded prognosis if his skin remains excessively moist over a period of several days after the onset or if he begins to manifest this characteristic after having been doing well.

CYANOSIS

Cyanosis is observed in a large proportion of persons suffering from myocardial infarction. In this series it was found in slightly over half of all the patients. In the study of Master and co-workers,[81] 29 per cent of those who died showed it, while only 9 per cent of those without it failed to recover. In our series, the mortality of those with cyanosis was 45 per cent, as contrasted with a mortality of 16 per cent for those without it. Cyanosis appeared with equal frequency and was of the same import in patients with anterior and in those with posterior lesions.

SHOCK

The patient who is suffering from acute myocardial infarction often presents the picture of shock. Fishberg, Hitzig and King[84] demonstrated that in persons undergoing their initial myocardial infarction the venous pressure and the circulating blood volume both tend to be those characteristic of shock. Other observers[40] have found that the appearance of peripheral circulatory collapse makes the prognosis more grave.

As with the manifestations of pain and dyspnea, the evidences of shock demonstrable for each patient in this series were classified as absent, mild, moderate or severe. Some degree of shock was present in 54 per cent of 205 patients. The mortality of those with shock was 44 per cent and for those without shock 28 per cent. The average degree of shock in those who died was definitely greater than in those who recovered. The mortality increased noticeably with higher degrees of shock, as the following figures show: absence of shock (95 patients), 20 per cent died; mild shock (57 patients), 26 per cent died; moderate shock (39 patients), 51 per cent died, and severe shock (14 patients), 93 per cent died. It was slightly greater in those with bundle branch block and those with partial or complete heart block than in those with other disturbances. There was a larger percentage of patients with posterior infarction who had severe shock than of those with anterior infarction. In judging the prognostic value of the degree of shock, the electrocardiographic changes afforded no additional aid.

CHARACTER OF HEART SOUNDS

Auscultation is usually more fruitful in cases of acute myocardial infarction than in cases of other forms of coronary arterial disease. Pericardial friction, gallop rhythm, various arrhythmias and the general quality of the heart sounds are all important signs for which search should be made. Gallop rhythm was present in 20 per cent of all

40. Levine.[10] Master, Dack and Jaffe.[81]

patients in this series. The mortality rate among patients with gallop rhythm was 43 per cent, as contrasted with that of 29 per cent for those without it, a result agreeing with the observation of Master and associates.[31] This abnormality appeared less frequently in patients with posterior infarction (13 per cent) than in those with an anterior lesion (22 per cent). However, when it did occur, it had a greater prognostic significance for patients with a posterior lesion than for those with an anterior lesion, the respective mortality figures being 62 and 33 per cent. As was to be expected, gallop rhythm was found in three fourths of the patients with bundle branch block.

The heart sounds were described as faint or muffled in 60 per cent of all patients. This abnormality also carries some prognostic import, for the mortality was 38 per cent in those who showed it as compared with 25 per cent in those who did not. This confirms the impression expressed by Middleton.[33] It occurred with equal frequency in association with anterior and with posterior infarction.

Auscultation over the precordial area in a patient who has suffered an acute myocardial infarction will often reveal a pericardial friction rub. This sign is often only transient, so that in some instances it will be missed unless frequent examinations are carried out. A search of the literature [41] for figures regarding the frequency with which a pericardial friction rub is heard after cardiac infarction yielded results ranging from 7 to 42 per cent. In our series there were 206 patients for whom the examination was considered adequate, and of these a pericardial friction rub was demonstrable in 16 per cent, usually some time during the first week after the initial symptoms of the attack. Previous reports are not in agreement as to the significance of a pericardial friction rub. Some authors [42] have expressed the belief that it did not influence the prognosis; others [29] have indicated that it occurred more commonly in those patients who died. In this series of patients, who were undergoing their initial attack of myocardial infarction, the mortality was 45 per cent for those in whom a friction rub was heard, while it was 31 per cent for those in whom this sign was absent.

Riseman and Harris [43] pointed out that pericardial friction can be detected, particularly when the infarcted area is located anteriorly. Of the 7 patients whose cases they reported, Vander Veer and Brown [19] observed this sign in 4 with anterior infarct and in 3 with a posterior

41. Coombs, C., and Ryle, J. A., in discussion on Cardiac Infarction, Lancet **1**:189 (Jan. 28) 1928. Howard.[13] Vander Veer and Brown.[19] Parkinson and Bedford.[28a]

42. Bedford.[30] Middleton.[33]

43. Riseman, D., and Harris, S. E.: Diseases of the Coronary Arteries with a Consideration of Data on the Increasing Mortality of Heart Disease, Am. J. M. Sc. **187**:1 (Jan.) 1934.

lesion. In our series of 33 patients who showed this abnormality, 28 had an infarction of the anterior portion of the left ventricle and 5 had a posterior lesion. Of the latter, 2 were examined post mortem. In both the antemortem localization of the infarct was confirmed. One of them had a terminal rupture of the posterior infarct. Thus, it may be said that although it is far more common in conjunction with anterior infarction, pericardial friction may be heard in patients who have suffered a posterior infarct and that this physical finding, of itself, does not localize the infarction. In addition, there were 4 patients in whom definite pericarditis was found post mortem but who had shown no pericardial friction. It is possible that the rub was overlooked or was too faint or too indistinct to be clearly distinguished.

It seems reasonable to state that the presence of pericardial friction indicates a significant area of myocardial infarction and in that sense would be accompanied by a somewhat graver prognosis than exists in many cases of the milder forms in which the area of involvement is smaller and does not reach the pericardial surface. However, a comparison of patients who are equally sick in other respects suggests that the presence of a friction rub probably has no significant effect on the outcome.

TEMPERATURE

It is a well recognized fact that fever of moderate degree usually appears in the course of myocardial infarction. The analyses of King,[27a] Master and co-workers[31] and Middleton[33] have indicated that if the fever is of high degree and long duration the outlook becomes unfavorable. Use of the highest rectal temperature not attributable to a complication during the course of the disease gave a similar result in the study of our patients with regard to fever. Rectal temperatures of 100 F. or more were observed in 93 per cent of all patients. In 84 per cent the highest temperatures fell between 100 and 102.9 F. In 6 instances the rise of temperature to levels of 104 F. or over was due solely to the cardiac lesion.

Among those patients who were observed during the first week of their illness, there were 10 whose rectal temperature never rose to 100 F. In fact, there were 3 whose rectal temperature did not reach 99 F., but 2 of these were patients in shock who did not survive long enough for the secondary evidences of infarction to develop. The other definitely had an anterior infarction, with classic electrocardiographic changes but without fever, leukocytosis, fall in blood pressure or any acceleration in the pulse rate. It seemed that some of the patients whose highest temperature ranged from 99 to 100 F. lacked the characteristic sudden onset and behaved as if the occlusion required several days to develop.

The mortality varied directly with the height of the temperature (table 3). For those whose highest temperature fell in the range between 100 and 102.9 F. (172 patients) the mortality was 29 per cent, while it was 64 per cent for those with temperatures between 103 and 103.9 F. (11 patients) and 83 per cent for those with elevations to 104 F. or over (6 patients). It was difficult to analyze the significance of the duration of fever because the time of first observation after the onset varied so much.

PULSE RATE

Conner and Holt [15] used the changes in pulse rate as one of the criteria of the severity of the attack. Master and co-workers [31] observed a mortality of 44 per cent for those with pulse rates of 120 or over, as contrasted with 10 per cent for those whose rate was never over 100 per minute. We have reviewed the case of each patient in our series for the highest pulse rate observed at any time during the acute phase

TABLE 3.—*Significance of Highest Rectal Temperature in One Hundred and Ninety-Nine Patients with Acute Myocardial Infarction*

Temperature (F.)	Number of Patients	Number of Deaths	Mortality, Percentage
Up to 99.9	10*	4†	40
100 to 100.9	68	14	21
101 to 101.9	54	18	33
102 to 102.9	50	18	36
103 to 103.9	11	7	64
104 and over	6	5	83

* Patients whose temperature fell in this zone were excluded if they were not observed during the first week of disease.

† Three of these 4 deaths were of patients who entered the hospital in severe shock and died within a few hours of the initial symptoms of the attack.

after the attack, excluding so far as possible those changes due to complications or to such arrhythmias as paroxysmal auricular fibrillation, paroxysmal ventricular tachycardia and heart block.

The average highest pulse rate for all patients was found to be 107 per minute. The average for those who survived was 104, as contrasted with 115 for those who died. Patients in whom the infarction involved the anterior wall of the left ventricle tended to have a higher rate than those with a posteriorly placed lesion. This is further brought out by the fact that 22 per cent of those with an anterior lesion had rates between 80 and 99, whereas 39 per cent of those with a posterior lesion fell into this zone. On the other hand, in 27 per cent of those with an anterior lesion the highest pulse rate ranged between 120 and 139, while the corresponding figure for those with a posterior lesion was only 13 per cent. The mortality for the entire series showed a progressive increase as the pulse rate rose, only 7 per cent of those with rates between 80 and 99 dying, as compared with 52 per cent of those

with rates over 120. Furthermore, there was evidence to suggest that when a pulse rate of over 120 is observed in a patient with a posterior infarct, the outlook is even more serious than it is when such a rate is seen in conjunction with an anterior lesion.

A pulse rate between 60 and 80 per minute in the absence of heart block is not incompatible with the presence of a myocardial infarction. Seven instances of such an association were seen in this series. In 1 case the infarction occurred while the patient was in the hospital. At no time was his pulse rate above 68, and an electrocardiogram three days after the acute attack showed evidence of an anterior infarct, with a pulse rate of 47 per minute but without signs of heart block. Such patients possibly have slow heart rates normally.

RESPIRATORY RATE

Analysis of the respiratory rate, the basis being the highest rate attributable to the infarction itself or to the pulmonary congestion resulting from it, gave results in accord on the whole with those of Master and co-workers.[31] The average highest respiratory rate for those patients who died was higher than that for those who survived. In addition, the mortality tended to rise directly with the respiratory rate. There was no significant variation within the several electrocardiographic groups in this respect. The actual respiratory rate, however, would seem to be of less value than other clinical observations.

LEUKOCYTE COUNT

Levine and Tranter[58a] and Libman[44] were among the first to point out the frequent appearance of leukocytosis in conjunction with other manifestations of acute coronary thrombosis. Other workers[45] have indicated that a high leukocyte count renders the outlook unfavorable. In our series the average highest leukocyte count for all patients was 15,000 per cubic millimeter, and, in addition, the average for those who lived was definitely lower (13,500) than that for those who died (18,800). Patients with anterior infarction tended to have a slightly higher leukocyte count (15,700) than those with a posterior lesion (14,200). Patients showing partial and complete heart block had the highest average leukocyte count (19,200), possibly because they had a larger area of heart muscle involved. The outlook appeared to be progressively more serious as the leukocytosis reached higher and higher levels. Of 118 patients with white blood cell counts under 15,000, only

44. Libman, E.: The Importance of Blood Examinations in the Recognition of Thrombosis of the Coronary Arteries and Its Sequelae, Am. Heart J. **1**:121 (Oct.) 1925.

45. King.[27a] Master, Dack and Jaffe.[31]

16 per cent died, while of 83 with leukocyte counts above that level 54 per cent died. This fact held equally true for each of the electrocardiographic groups. It should be pointed out, furthermore, that 14 per cent of the patients had leukocyte counts below 10,000 during the first week following the initial onset of symptoms, and in 3 per cent the level was over 30,000 at some time in the course of the attack. Thus neither marked leukocytosis nor a normal white cell count is incompatible with the diagnosis of myocardial infarction. Although fever and leukocytosis generally go together, either one may be present in the absence of the other during the first week following an acute attack of coronary thrombosis, and rarely are both absent.

SEDIMENTATION RATE

Among the more recent observations in cases of myocardial infarction has been the frequency with which the sedimentation rate becomes elevated. Rabinowitz and co-workers [46] were the first to appreciate this change and felt that it might well be a good index of the progress of healing of the area of myelomalacia due to a coronary occlusion. Gorham and Thompson [47] obtained little information concerning prognosis from the determination of this factor. Unfortunately, the information regarding sedimentation rates in our series was not complete. The test was carried out for one fourth of all patients, but for most of them serial observations were not made. It may be said, however, from the data available that the height of the sedimentation rate would seem to have scant prognostic value. The test occasionally had value as a diagnostic procedure, particularly in cases in which clinical and electrocardiographic findings were equivocal.

CONGESTIVE FAILURE

Pulmonary Congestion and Acute Pulmonary Edema.—Pulmonary congestion is a common concomitant of acute coronary thrombosis. It may range from merely a few rales at the base of the lung to coarse rales throughout the entire pulmonary field, with an associated sense of suffocation on the part of the patient. We have reviewed the cases of our entire series of 206 patients in which the information was complete in this regard and have designated the congestion as one of four degrees: (1) absent (no rales), (2) mild (a few basal rales), (3) moderate (many rales, without respiratory distress) and severe (generalized rales, with suffocation). Only the pulmonary changes present during the first

46. Rabinowitz, M. A.; Shookoff, C., and Douglas, A. H.: Red Cell Sedimentation Time in Coronary Occlusion, Am. Heart J. **7**:52 (Oct.) 1931.

47. Gorham, L. W., and Thompson, H. C.: A Study of Erythrocyte Sedimentation Rate and Differential Leucocyte Count in Coronary Occlusion, Internat. Clin. **1**:44 (March) 1938.

day or so were analyzed, as it is obvious that congestion will be extremely common as a terminal manifestation. From this analysis it was learned that the average degree of pulmonary congestion in the patients who died was twice as great as that in those who recovered. With but few minor exceptions, this held true no matter what the electrocardiograms showed. The average degree of pulmonary congestion in patients with anterior infarction and in those with posterior infarction was the same. Patients with bundle branch block had, on the whole, more extensive pulmonary changes than patients in any of the other electrocardiographic groups.

Of the series as a whole, 29 per cent had no evidence of pulmonary congestion, 39 per cent had it to a mild degree, in 15 per cent it was moderate and in 16 per cent it was severe. Among the patients who died, only 9 per cent showed no rales and 55 per cent had moderate or marked evidence of congestion. Of all patients studied, pulmonary congestion was absent most frequently (50 per cent) in those having electrocardiograms of the unclassified type.

TABLE 4.—*Significance of Degree of Pulmonary Congestion in Two Hundred and Six* Patients with Acute Myocardial Infarction*

Degree	Number of Patients	Number of Deaths	Mortality, Percentage
Absent	58	6	10
Mild	82	25	30
Moderate	32	14	44
Severe	34	23	68

* Data regarding this point were considered inadequate for 2 patients.

The rather important prognostic significance of the degree of pulmonary congestion was brought out further by the mortality for each of the four degrees (table 4): absent, 10 per cent; mild, 30 per cent; moderate, 44 per cent, and severe, 68 per cent. Here, again, this clinical feature was of nearly the same importance in each electrocardiographic group.

It is not at all uncommon for a person suffering from an acute myocardial infarction to exhibit what is commonly termed acute pulmonary edema or acute left-sided heart failure either at the onset of his attack or during the first few days after the initial symptoms appear. Such persons obviously fall into the group designated in the preceding paragraph as having severe pulmonary congestion. In our series this clinical picture was observed in 13 per cent of all patients. It was equally common in those with an anterior lesion, in those with posterior infarction and in those showing partial and (or) complete heart block. It was far more frequently seen, however, in patients with bundle branch block, being present in over one half. When this clinical phenomenon occurred it was of grave importance inasmuch as it carried

a mortality of 64 per cent, as contrasted with a mortality of 28 per cent for those who did not show it. It was even more serious in the presence of a posterior infarction, for 7 out of 8 patients with that type of lesion and acute pulmonary edema died as compared with 7 among 12 patients with anterior infarction and acute left-sided heart failure.

It is clear from this study that significant pulmonary congestion during the early days after an attack of acute coronary thrombosis materially increases the gravity of the outlook.

Palpable Liver and Peripheral Edema.—It is not uncommon for acute coronary thrombosis to be followed by acute hepatic engorgement, with the result that physical examination within the first few days of illness will reveal a palpable liver. For the most part hepatic enlargement is apt to occur after six to ten days has elapsed. In this series the liver was reported as palpable in 29 per cent of all patients. It is true, however, that in some this physical finding may have been present prior to the acute infarction. Libman [48] has suggested that enormous acute engorgement of the liver should lead one to suspect thrombosis of the right coronary artery. This supposition was not borne out in our study. Of the 6 patients examined post mortem who showed thrombosis of one of the branches of the right coronary artery 2 had a palpable liver, and of the 23 with involvement of the left coronary artery the liver was felt in 10. In fact, there were some patients with involvement of the left coronary artery observed at autopsy who showed an enlarged liver and who died within the first forty-eight hours. A palpable liver was frequently observed in patients with bundle branch block (5 out of 9) and was slightly more commonly associated with posterior infarction (21 out of 64) than with an anterior lesion (29 out of 108). In the entire series, the finding of a palpable liver proved to be of only slight prognostic value, since the mortality was 40 per cent when it was present and 30 per cent when it was absent.

As is the case with hepatic engorgement, peripheral edema may often make its appearance a few days after the initial manifestations of myocardial infarction. This occurred in 22 per cent of our total of 208 patients. When it did appear it was of some gravity, for the mortality for patients with edema was 50 per cent as compared with that of 28 per cent for patients without edema. As was the case with a palpable liver, peripheral pitting was slightly less commonly associated with anterior infarction (21 per cent) than with a posterior lesion (25 per cent) or with bundle branch block (33 per cent). When it did develop, however, it was of greater significance in patients with anterior infarc-

48. Libman, E.: Some Observations on Thrombosis of Coronary Arteries, Tr. A. Am. Physicians **34**:138, 1919.

tion, for 61 per cent of them died as compared with 22 per cent of those with such a lesion but without edema. On the other hand, among patients with posterior infarction, the mortality was only slightly higher (44 per cent) for those with edema than for those without it (33 per cent).

Thus it may be said that, though a palpable liver and (or) peripheral edema are less common in conjunction with anterior infarction than with a posterior lesion or with bundle branch block, when they do occur the outlook is graver for patients with the first condition than for those with either of the last two.

Right and Left Heart Failure.—In our series, some physical signs of congestive failure occurred in 72 per cent of all patients and tended to be somewhat more common and more severe in those who had had previous hypertension. This finding is in accord with the observations of other workers.[31] It is clear that congestive failure makes the outlook in myocardial infarction more grave, for those who showed evidences of decompensation had a mortality of 41 per cent as contrasted with a mortality of 12 per cent for those who did not. Left heart failure alone occurred in 40 per cent of all patients and carried a mortality of 36 per cent. Right heart failure alone occurred in only 2 patients (1 per cent), both of whom recovered. Right and left heart failure together appeared in 31 per cent of all patients, of whom 49 per cent died.

Pletnew [49] and Kohan and Bunin [50] have indicated that right heart failure points to thrombosis in the right coronary arterial system. Fishberg and his co-workers [34] have stated that "it has not seemed that the type of circulatory failure present permits, of itself, the differentiation between right and left coronary occlusion." On the whole, our findings have been in agreement with the latter view. Considering left heart failure alone, we found it occurred slightly more commonly in association with anterior infarction (44 per cent) and with partial or complete block (57 per cent) than with posterior infarction (35 per cent) or with bundle branch block (33 per cent). However, when it did occur, it rendered the prognosis somewhat more serious for the patients with a posterior lesion, for 48 per cent of them died as compared with 42 per cent of those with an anterior lesion. Right heart failure alone developed in only 2 patients, both of whom had posterior infarction and both of whom survived. Right and left heart failure together occurred with almost the same frequency in patients with anterior infarction (31 per

49. Pletnew, D.: Zur Frage der intravitalen Differentialdiagnose der rechten und linken Coronararterienthrombose des Herzens, Ztschr. f. klin. Med. **102**:295, 1926.

50. Kohan, B. A., and Bunin, E. I.: Zur Frage über die Differentialdiagnose der Thrombose der rechten und der linken Kranzarterie des Herzens am Lebenden, Ztschr. f. Kreislaufforsch. **20**:199 (April) 1928.

cent) as in those with a posterior lesion (32 per cent). It was more commonly seen in patients with bundle branch block (55 per cent). Decompensation of this type had a somewhat greater significance in patients with an anterior lesion, for 52 per cent of them died as compared with 45 per cent of those with a posterior lesion and both right and left heart failure.

Fishberg and associates [51] expressed the opinion that severe right heart failure pointed to involvement of the intraventricular septum by the infarction. In our series, 36 patients were examined post mortem. (In 1 additional patient the statement regarding the septum was inadequate.) Of 20 patients with right and left heart failure, 14 had septal involvement and 6 did not. In 13 patients with left heart failure alone, 7 showed extension to the septum, whereas it was absent in 6. Three patients died without showing any clinical evidence of congestive failure; 2 of them were found to have areas of infarction which included portions of the septum. It may be said, then, that although the development of right and left heart failure may suggest involvement of the septum, the relation is not close enough to be clearly diagnostic.

From the foregoing data it follows that some form of congestion, especially that of the left ventricle, occurred in about three fourths of the patients and was more common in those with hypertension. Early pulmonary congestion was least frequent in the patients who recovered, and the mortality increased progressively with the more severe degree of congestion. The location of the infarct either anteriorly or posteriorly did not influence the degree of pulmonary congestion. Failure of the right side of the heart as evidenced by a palpable liver and by peripheral edema was slightly more commonly associated with posterior than with anterior infarction, but when it did occur, the outlook was more grave for the patients with an anterior lesion.

COMPLICATIONS

The progress of a patient who has suffered an acute myocardial infarction may at any time become complicated by any one of a number of grave situations. They play no small part in rendering the disease as serious as it is. In this study we have included in the mortality statistics those patients in whom the picture was complicated by intercurrent disease or by situations which we feel would not have supervened had the patient not had the original acute coronary thrombosis. The incidence and significance of the more common and important complications will be discussed.

51. Padilla, T., and Cossio, P.: Pronóstico del infarto de miocardio, Rev. argent. de cardiol. **1**:181 (July-Aug.) 1934.

Pulmonary infarction occurred in 8 per cent of all patients, with a mortality of 53 per cent, as compared with that of 31 per cent for those patients showing no evidence of this complication. It is well recognized that intramural thrombi frequently form over the endocardium of an area of cardiac infarction. Since infarction almost always occurs in the left ventricle, a thrombus can form in the right ventricle only if there is extension to the interventricular septum or to the myocardium of the right ventricle. Such a thrombus can then serve as the source for pulmonary emboli. Of the 9 patients in our series who died after an illness complicated by pulmonary infarction, 8 were examined post mortem. Of these, only 2 showed a thrombus over the right surface of the interventricular septum. A third patient had an infarct which involved only the right anterior ventricular wall, and a large intramural thrombus was found over it. This patient showed thrombosis of the right coronary artery. In the remaining 5 patients no source of pulmonary emboli could be found in the heart. It is well known that two other mechanisms are commonly responsible for pulmonary infarction in cardiac disease, i. e., local thromboses of pulmonary vessels and phlebitis with thrombosis of the veins of the pelvis and legs. These two mechanisms very likely explain the infarction in the aforementioned 5 patients.

Such factors as the advanced age of many of the patients, the enforced rest in bed, the pulmonary congestion and the sedation and narcosis necessary for relief of distress may lead to the development of pneumonia in persons who have had acute coronary thrombosis. In our series, this complication arose in 9 per cent of the patients. Its grave significance is indicated by the fact that 89 per cent of those in whom it appeared succumbed. It was equally common in patients with anterior and in those with posterior infarction.

The course of many patients with acute myocardial infarction is complicated by the appearance of a psychic disturbance, a hallucinatory or delusional state. Such mental disturbances occurred in 7 per cent of all patients in this series. Levine [10] and Middleton [33] have reported that such a development renders the outlook less favorable. This was confirmed in our series, for those patients whose course was complicated in such a manner had a mortality of 60 per cent, as compared with a mortality of 31 per cent for those who showed no disturbance in the psyche.

Cerebral vascular accidents constitute another complication. They may result from cerebral hemorrhage, cerebral thrombosis or cerebral embolism. There were 9 patients in this series who showed evidence of cerebral vascular accident. Seven of them succumbed, an indication of the gravity which obtains in such a complication. Because

of the great frequency of intramural thrombus formation in the left ventricle over the infarcted area, a cerebral embolism is a particular hazard. Of the 37 patients who were examined post mortem, 14 showed a left ventricular mural thrombus, and in 3 of these there was also a thrombus in the right ventricle. One additional patient showed only a right ventricular mural thrombus. There were 3 patients with an auricular thrombus, none of whom had valvular disease; 2 of them are included with the aforementioned 14 patients with left ventricular thrombi, and the third had no other thrombi.

Other complications which would appear to make the outlook more serious include renal infarction, which occurred in 3 patients, with 2 deaths, and splenic infarction, which developed in 6 patients, with 5 deaths. Embolism of the arteries of the limbs seems to be less frequent, as in only 1 case was this recognized clinically. Of the 37 patients postmortem examination of whom was permitted, a myocardial rupture, occurring three and a half, eleven and fifteen days, respectively, after the onset, was demonstrated in 3. In 1 case a clinical diagnosis of ruptured intraventricular septum was made in a patient who had an anterior infarction and in whom while in the ward a loud systolic murmur developed. This patient died, but permission for autopsy was not granted. Although sudden death during acute coronary thrombosis is often due to a rupture of the ventricle, this is not always the case. There were several cases in which death came abruptly, in 2 of which no rupture could be found on postmortem examination. Such instantaneous fatalities may occur during the first week or so after the onset of the attack, even when the patient seems to be doing well. In some, but not all, instances of sudden death not due to rupture, an antecedent heart block may have been present.

Six patients of the entire series showed definite evidence of valvular heart disease. Two of them had aortic stenosis; both died, and the diagnosis was confirmed at autopsy for the 1 for whom postmortem examination was allowed. Two patients had mitral stenosis and insufficiency; 1 of them succumbed, and postmortem examination confirmed the diagnosis. One patient had both mitral stenosis and insufficiency and aortic stenosis and insufficiency. He had a myocardial infarction at the age of 39 and recovered satisfactorily. One patient had syphilitic aortic insufficiency and recovered, despite an onset characterized by both acute pulmonary edema and paroxysmal auricular fibrillation. It would appear from even this small number of patients that acute coronary thrombosis does occur in the presence of valvular disease and that the outlook for recovery of patients with such a condition is approximately 50 per cent.

ARRHYTHMIAS

Abnormalities of the cardiac rhythm occur with great frequency during acute coronary thrombosis. These are of a wide variety, and it will be our purpose here to discuss only the major disturbances observed in this series. Of all the patients, 38 per cent showed some arrhythmia. In many instances the same patient showed two or three different types of deranged cardiac mechanisms at different times. Patients who showed some disturbance of cardiac rhythm had a mortality of 42 per cent, as compared with a mortality of 27 per cent for those who did not, a finding which is in agreement with the observations of Middleton,[28] Padilla and Cossio [51] and Master, Dack and Jaffe.[52]

The analysis of the cases of those patients who showed auricular fibrillation was particularly interesting. Levine [10] has pointed out that patients with persistent auricular fibrillation rarely have subsequent myocardial infarction. He reported that its occurrence during a myocardial infarction does not appreciably alter the prognosis and that, though usually transient, the fibrillation may persist after recovery. In this series auricular fibrillation occurred in 25 patients (12 per cent). Its presence did not influence the outlook greatly, since 36 per cent of this number died, as compared with a mortality of 32 per cent among all other patients. There was definite evidence that in 20 instances the fibrillation was transient. Two patients died soon after the first appearance of this arrhythmia, so that no opportunity was afforded to learn whether it would persist. Of the remaining 3 patients, 2 had auricular fibrillation both on admission to the hospital and on discharge after recovery, and it was impossible to tell when the irregularity first appeared. In only 1 case electrocardiograms taken before and after the acute attack yielded definite proof that persistent auricular fibrillation developed in conjunction with the myocardial infarction. Auricular fibrillation was slightly more common in patients with anterior infarction (15 out of 109) than in those with a posterior lesion (5 out of 63), but it carried a somewhat graver prognosis for the latter.

That paroxysmal ventricular tachycardia is not infrequently associated with acute coronary thrombosis was observed as early as 1921 by Robinson and Herrmann.[8a] In this series there were 6 patients (3 per cent) in whom it was known to appear. All had infarction of the anterior part of the left ventricle, and one half of them succumbed. Paroxysmal auricular flutter occurred in 5 patients. One had a posterior infarct, and 4 had an anterior lesion. Three of them died. Premature beats of various types were common. In this series they occurred in 52

52. Master, A. M.; Dack, S., and Jaffe, H. L.: Disturbances of Rate and Rhythm in Acute Coronary Artery Thrombosis, Ann. Int. Med. **11**:735 (Nov.) 1937.

patients. The majority showed premature ventricular beats or premature auricular beats. Premature nodal beats and blocked premature auricular beats were less common. Extrasystoles did not alter the prognosis materially (33 per cent mortality). Auriculoventricular nodal rhythm was observed in 6 instances, and in 4 of these the patient did not recover. It is worth while to note here that in spite of the great variety of arrhythmias encountered in this series, we have found no instance of paroxysmal auricular tachycardia. Master and co-workers [82] reported 3 cases in a group of 300 patients. It is our impression that this particular type of disturbed cardiac mechanism must be extremely rare in association with acute myocardial infarction.

In this paper we have grouped partial heart block and complete heart block together, for it was observed that patients showing one of these alterations commonly were found to show the other at some later time. There were 7 patients who fell into this particular group. It was striking that in none who survived after the first few days did the original degree of block persist. Two patients went through all three degrees of block and showed a normal mechanism on recovery. One showed 2:1 block, then a lesser degree of partial block, then simple delayed auriculoventricular conduction and finally a normal mechanism. Another patient showed, first, complete heart block and then delayed auriculoventricular conduction, which persisted. Still another showed this same change and then reverted to a 2:1 partial heart block, which persisted. It follows, therefore, that once heart block develops in association with acute myocardial infarction, if the patient survives, complete recovery from the block or a lesser degree of block tends to be the ultimate outcome. Among these patients, 5 had complete heart block at one time or another, and of these, 2 manifested Adams-Stokes attacks.

It is the general impression that partial or complete heart block is more commonly associated with posterior infarction than with an anterior lesion. The number of patients in this study was small but did show a trend in that direction, 4 having posterior infarction and 3 having a lesion located anteriorly. In order to learn if this relation would be borne out in a larger group we reviewed the cases of all patients seen at this hospital in the past ten years who had either partial or complete block in association with acute coronary thrombosis. The addition of these patients to those included in our present series made a total of 29. Of these the evidence pointed to posterior infarction in 20 and anterior infarction in 9. It was interesting to note that in this larger series, also, there was a definite tendency for the degree of block originally present to diminish, so that of the total of 19 patients who survived, 10 showed a normal cardiac mechanism at the time of discharge.

SUMMARY AND CONCLUSION

A study was made of the cases of 208 patients with acute coronary thrombosis observed consecutively at the Peter Bent Brigham Hospital. So far as could be judged clinically, only those patients were included whose attacks were regarded as initial. The findings present during the early hours or few days were those which were particularly analyzed, which course thereby eliminated the obvious terminal changes that so often predict fatality. The purpose of this investigation was to determine whether any of the findings during the early part of the illness can serve as a guide to prognosis. The significance of individual clinical and electrocardiographic features was therefore analyzed, with the following results:

Mortality.—The immediate mortality in the entire series was 33 per cent. Anterior infarctions occurred more commonly than posterior lesions, the proportion being 5:3, but the mortality was about the same with regard to the two locations. The mortality was distinctly higher for patients with bundle branch block and those with auriculoventricular block, but lower for those who showed low voltage of the QRS complex. A group that had electrocardiographic findings which were regarded as unclassifiable, i. e., without significant changes or abnormalities, also had a distinctly lower mortality.

Sex.—The proportion of men to women was 7:3. The prognosis for women was somewhat more grave.

Age.—The average age at the time of the attack was 58.7 years for the entire series—57.4 years for men and 61.5 years for women. The mortality progressively increased with advancing years. This held true regardless of the electrocardiographic findings.

Previous Angina Pectoris.—Antecedent angina pectoris was present in 72 per cent of all patients and was equal in its occurrence in the two sexes. Those patients with a previous history of such a condition had a lower mortality (29 per cent) than those without it (38 per cent).

Previous Hypertension.—Antecedent hypertension was present in 57 per cent of all patients, 44 per cent of the men, and 86 per cent of the women. It tended to increase the mortality in both sexes. Coronary occlusion in women who had neither previous angina pectoris nor hypertension was particularly rare.

Blood Pressure Changes.—The occurrence of a fall in systolic blood pressure of more than 20 mm. increased the mortality slightly, although a systolic level that was maintained below 80 mm. for many hours or days appeared to be serious.

Pain.—The severity or radiation of the pain had but little prognostic value, nor did it aid in the localization of the infarction. However, in

the small number of patients without pain in the chest there was a mortality decidedly higher than average. Anterior infarction with pain radiating to the left arm had a lower mortality (20 per cent) than similar infarction without this radiation (41 per cent). Radiation of pain to the right arm, as well as to the left, was slightly more common in association with posterior infarction. The occurrence of initial attacks of myocardial infarction without any pain or its equivalent symptoms was rare (3 per cent).

Dyspnea.—Dyspnea of some degree occurred in 71 per cent of patients. The mortality increased decidedly as dyspnea became more prominent, from 18 per cent for those with no dyspnea to 24, 36 and 62 per cent for those with mild, moderate and severe dyspnea, respectively. Dyspnea was much more helpful than pain in judging the prognosis.

Sweating.—Sweating occurred commonly but was of only slight prognostic significance. However, the presence of a moist skin days or weeks after the onset appeared to indicate that the dangerous period had not yet passed.

Cyanosis.—Cyanosis was found in about one-half the patients and indicated a distinctly higher mortality (45 per cent as compared with 16 per cent).

Shock.—Some degree of shock was present in 54 per cent of all patients. The mortality increased in direct proportion to the degree of shock: absent, 20 per cent; mild, 26 per cent; moderate, 51 per cent, and severe, 93 per cent.

Auscultatory Signs.—Gallop rhythm was noted in 20 per cent of all patients and was more common among those who died. It was more commonly associated with anterior than with posterior infarction, but was a more serious sign for patients with the latter lesion. The quality of the heart sounds was regarded as faint in over one-half the patients, and such sounds were more common in those who succumbed. The incidence of pericardial friction rub was 16 per cent. Although generally associated with anterior infarction, it was observed in 5 patients with a posterior lesion. Its appearance renders the outlook somewhat more grave (45 per cent, as compared with 31 per cent).

Temperature.—The rectal temperature was above 100 F. in 92 per cent of the patients. In 7 instances it was between 99 and 100 F. and in 3 it was below 99 F. There was a distinctly progressive rise in mortality with the increasing levels of fever.

Pulse.—When changes in the pulse rate due to such arrhythmias as paroxysmal rapid heart action and heart block were excluded, the heart rate in the great majority of patients was over 100 (average, 107). In

7 patients, however, the rate never rose above 80, and in 1 it was under 70. A slight tendency to increased mortality accompanied the more rapid rates.

Respiratory Rate.—The respiratory rate, in general, followed the pulse rate and the degree of dyspnea and was on the whole more rapid in the patients who died than in those who recovered.

Leukocyte Count.—A leukocyte count over 10,000 during the first week following the onset of the attack was found in 86 per cent of the patients. In 3 per cent the count was over 30,000. The mortality was 16 per cent for those with counts under 15,000 and 54 per cent for those with counts over that level.

Sedimentation Rate.—Although data concerning sedimentation rates were not numerous, the rates did not seem to be of much prognostic value.

Congestive Heart Failure.—About three fourths of the patients showed some objective evidence of congestive failure. The mortality steadily increased with increasing degrees of pulmonary congestion: absent, 10 per cent; slight, 30 per cent; moderate, 44 per cent, and marked, 68 per cent. A palpable liver was found in 29 per cent of the patients. This appears more frequent than one would expect in initial attacks of acute coronary thrombosis but probably reflects the greater gravity of conditions in patients coming to a public hospital. The presence of a palpable liver increased the mortality slightly. Peripheral pitting edema occurred in 22 per cent of the patients and was definitely associated with increase in the mortality (50 per cent with pitting as contrasted with 28 per cent without). Left heart failure occurred more commonly, but was slightly less serious with anterior than with posterior lesions. The combination of both right and left heart failure was equally common with anterior and with posterior infarction. It did seem that the presence of right heart failure was somewhat more serious in patients with an anterior lesion.

Complications.—Such complications as pulmonary infarction, pneumonia, psychosis, cerebral vascular accident and peripheral arterial embolus obviously made the outlook more serious. Among 37 patients examined post mortem, there were 3 with rupture of the ventricle and 15 with ventricular mural thrombosis. Six patients in this entire series had additional valvular disease. Sudden, unexpected death while patients were apparently doing well was found in some instances to occur without myocardial rupture.

Arrhythmias.—Some type of arrhythmia was observed in 38 per cent of these patients and tended to increase the mortality to a slight extent. Auricular fibrillation, almost always of the transient type, occurred in

12 per cent of the patients, paroxysmal ventricular tachycardia in 3 per cent (all with anterior infarction), paroxysmal auricular flutter in 2.5 per cent and extrasystoles of some form in 25 per cent. There was not a single instance of paroxysmal auricular tachycardia. Partial or complete heart block was present in 3.5 per cent of the patients and was more commonly associated with a posterior than with an anterior lesion. The degree of block tended to decrease or disappear if recovery occurred.

Electrocardiograms.—In a review of the electrocardiographic data in this study it appeared that the absence of any significant changes in the tracings indicated a distinctly more hopeful immediate outlook. When distinctly abnormal alterations in the ventricular complex were found, with few exceptions, it did not seem to matter greatly what they were, apart from important arrhythmias.

Conclusion.—It can be stated that the immediate outlook in a case of acute coronary thrombosis is extremely difficult to predict. Although many of the clinical and electrocardiographic features analyzed may indicate that the condition is either more or less critical, there is practically no criterion which is infallible. However, weighing all the information available together with the general appearance of the patient enables the physician to make a fair estimate as to the immediate prognosis.

IMPORTANCE OF THE DEXTROSE TOLERANCE TEST IN THE DIAGNOSIS OF MARGINAL MALNUTRITION

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The possibility of marginal malnutrition in so-called normal persons has been a subject of increasing interest in recent years. When malnutrition has reached the point where definite deficiency disease or marked wasting and dehydration have developed, the diagnosis is easy. In the prodromal states, however, no method has been presented whereby malnutrition can be determined except from the history or by the rather complex quantitative analysis for vitamins or other factors, i. e., procedures which are not very specific and which present technical difficulties to the practicing physician.

The diagnosis of developing malnutrition is an important one, especially in the case of the nervous type of patient, because malnutrition produces easy fatigability which, in turn, increases the severity of the subjective symptoms, such as nervous tension and irritability. An exact diagnostic procedure would be of great benefit not only in dealing with patients of the nervous type but in the general practice of medicine. We believe that the dextrose tolerance test, if properly interpreted, is such a procedure.

The high incidence of diabetic-like dextrose tolerance curves among patients of the nervous or mental type has been reported recently by Robinson and Shelton.[1] In order to try to determine the etiologic basis of these curves, which indicate disturbance in the ability to utilize and metabolize dextrose for energy, certain cases were selected from the original series for careful analysis to determine if they had a common etiologic denominator. We selected 5 cases which, according to three criteria proposed for the diagnosis of diabetes by tolerance curves, were instances of "diabetes mellitus," yet all the curves returned to "normal"

From Neurological Hospital.

1. Robinson, G. W., Jr., and Shelton, P.: Incidence and Interpretation of Diabetic-Like Dextrose Tolerance Curves, J. A. M. A. **114**:2279 (June 8) 1940.

within a relatively short period. We also selected 2 cases with normal curves for comparison.

The three criteria by which the diagnosis of diabetes mellitus may be established by tolerance curves are those described by (1) Exton and Rose [2]; (2) Gould, Altshuler and Mellen,[3] and (3) Matthews, Magath, Berkson and Gage.[4]

According to Exton and Rose, a diabetic tolerance curve is established when (1) a more or less steep rise of not less than 10 mg. of blood sugar following the second dose of dextrose is present and (2) "the relation of blood and urine sugar values to the severity of the disease" is given consideration.

The establishment of a diabetic tolerance curve by the criterion of Gould and co-workers is indicated when there are "(1) a fasting blood sugar which exceeds 120 mg. per hundred cubic centimeters; (2) a half-hour blood sugar which exceeds the fasting level by 50 mg. or more, and (3) a one hour blood sugar which exceeds the half-hour level by 30 mg. or more." When two of these three conditions are present, the diagnosis of diabetes mellitus can be made, according to the authors.

According to Matthews and co-workers:

> If 158 mg. per hundred cubic centimeters of blood is taken as the critical level so that individuals showing a blood sugar reading below this level at the hour are designated nondiabetic and individuals with readings at or above this value are designated presumptively diabetic, a high percentage of correct diagnoses can be expected. As far as the observations in this series are concerned, all individuals with values at the hour less than 154 mg. were found to be normal, and all individuals with values at the hour of 180 mg. or more were found to be diabetic.

Two of us presented in a previous paper [1] case analyses which showed that according to Exton and Rose 60.8 per cent, according to Gould and co-workers 36.3 per cent and according to Matthews and associates 54.5 per cent of our consecutively admitted patients could be given the diagnosis of diabetes or presumptive diabetes.

In selecting 5 of the cases for this study, we adhered strictly to these criteria and took only those cases in which the patient's condition could be diagnosed as diabetes mellitus by all three standards. These cases

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2. Exton, W. G., and Rose, A. R.: Diabetes as a Life Insurance Selection Problem, Proc. A. Life Insur. M. Dir. America (1931) **18**:252, 1932; The One-Hour Two-Dose Dextrose Tolerance Test, Am. J. Clin. Path. **4**:381, 1934.

3. Gould, S. E.; Altshuler, S. S., and Mellen, H. S.: The One-Hour Two-Dose Glucose Tolerance Test in the Diagnosis of Diabetes Mellitus, Am. J. M. Sc. **193**:611 (May) 1937.

4. Matthews, M. W.; Magath, T. B.; Berkson, J., and Gage, R. P.: The One-Hour Two-Dose Dextrose Tolerance Test (Exton-Rose Procedure), J. A. M. A. **113**:1531 (Oct. 21) 1939.

were selected to show that, although the patients had definite diabetic curves, the curves probably indicated malnutrition. With proper treatment, these curves returned to normal, and since discharge these patients have maintained normal carbohydrate metabolism without treatment. We shall endeavor to show by analysis of cases a common etiologic denominator, namely, malnutrition.

Cases of mental conditions of various types make up our material. Patients with such conditions are excellent material for studies in malnutrition, especially of the marginal type, because their habits and symptoms lead to this state and these physiologic abnormalities will

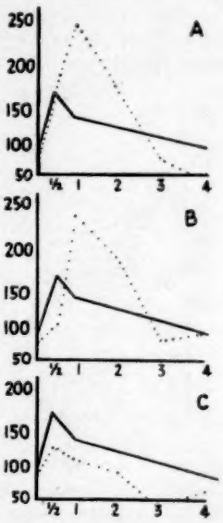

Fig. 1.—Dextrose tolerance curves for F. P. (case 1) obtained (*A*) Sept. 2, 1939, the day following admission to the hospital, (*B*) October 18, forty-six days after the first test, and (*C*) November 13, seventy-two days after the first test.

develop in any person who suffers from malnutrition. These interpretations are in the field of internal medicine. The underlying psychiatric factors are, we believe, incidental in this presentation.

Case 1.—F. P., a white woman aged 32, was admitted to the hospital Aug. 30, 1939 with the chief complaint of negativism. The onset of her condition, which followed severe financial worry and strain, coupled with the birth of 2 children, began approximately three years before. Until two weeks before admission to the hospital she was in a state of profound agitation and depression, which had progressed since its onset some three years before to an acute condition. During this interval the patient lost 15 pounds (6.8 Kg.). That her metabolic processes were seriously impaired was indicated by the fact that for several weeks after entrance to the hospital she continued to lose weight, despite the fact

that she received insulin and intravenous injections of dextrose and ate 100 per cent of her regular diet. Previous to admission the patient never reached the state in which she refused food, but it was apparent from the loss in weight that she received little energy value from her food. At the time of examination she was hyperactive and agitated, and her activity continued for two weeks. Physical examination revealed nothing which suggested a pathologic cellular condition. The red cell, the white cell and differential counts of the blood were normal, and chemical studies on September 1 revealed that the nonprotein nitrogen was within the normal range and the fasting blood sugar was 72.7 mg. per hundred cubic centimeters. There were traces of sugar and albumin in the urine. The patient's dextrose tolerance curve is illustrated in figure 1 *A*. The fasting blood sugar, as shown, was 82.0 mg. per hundred cubic centimeters on September 2. At the one-half hour interval the blood sugar had risen to 175.4 mg. and at the one hour mark to 250.0 mg.; by the fourth hour it had fallen to 48.4 mg. The urine gave a 2 plus reaction for sugar both at the end of the first hour and at the end of the test. This curve, by all three criteria outlined, is characteristic

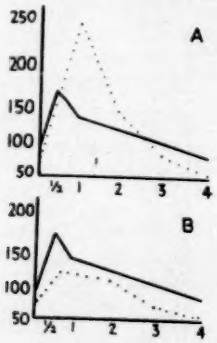

Fig. 2.—Dextrose tolerance curves for M. P. (case 2) obtained (*A*) Sept. 3, 1939, the day following admission to the hospital, and (*B*) November 8, thirty-five days later, during which period insulin and metrazol shock therapy was given.

of diabetes. The test was repeated on October 18 and on November 13. On the former date the curve was much the same as on September 2, but on the latter date it was normal; it has remained so since her dismissal from the hospital.

On September 4 the patient began receiving metrazol and insulin shock therapy. In all she had twelve metrazol shock reactions. She began to improve two weeks after entrance into the hospital and was discharged October 25. Her condition since discharge has been excellent; she is enjoying the best of health and has had a complete psychiatric remission.

Case 2.—M. P., a white woman aged 34, was admitted to the hospital Sept. 2, 1939, with the chief complaint of fear and anticipation of future events. In 1931 she had had an appendectomy, and later Malta fever developed. After that she became cachectic and was given small doses of insulin to stimulate appetite. She began to lose weight; her condition became progressively worse, and on her admission to the hospital she weighed 81½ pounds (37 Kg.). Examination at the time of admission revealed a person of slight build who had apparently lost considerable weight and manifested few signs of activity. No other gross abnor-

malities were apparent. There was a trace of sugar in the urine. The white blood cell count was 11,875, with a normal red cell count. Chemical studies of the blood gave a sugar value of 65.6 mg. per hundred cubic centimeters and a nonprotein nitrogen value within normal limits. The cholesterol content of the blood was 226 mg. per hundred cubic centimeters. The dextrose tolerance curve, as shown in figure 2 *A*, was a typical diabetic curve, according to the criteria. From a fasting level of 65.6 mg. per hundred cubic centimeters the blood sugar rose to 250.0 mg. at the one hour interval, and by the fourth hour it had dropped to 55.6 mg. A trace of sugar was found in the urine at the end of one-half hour, and the reaction was 3 plus and 4 plus at the one and two hour periods, respectively. No sugar was present in the four hour sample. This test was run the day after admission, and the resultant curve conforms to all three criteria of a diabetic curve. The patient's condition was diagnosed as schizophrenia, and she was given insulin and metrazol shock therapy. Approximately four weeks was required to improve her physical condition to the point where she could undertake these treatments with safety. On November 8, before her discharge

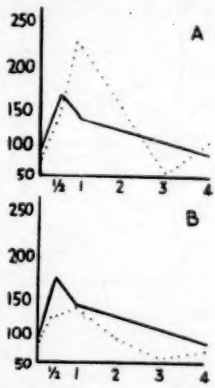

Fig. 3.—Dextrose tolerance curves for J. C. (case 3) obtained (*A*) Sept. 5, 1939, the second day following admission to the hospital, and (*B*) October 16, forty-one days later, during which period metrazol shock therapy was given.

from the hospital, another dextrose tolerance test was run. We found the curve to be normal. Her fasting blood sugar level was 69.0 mg. per hundred cubic centimeters. The next sample showed the peak at 133.3 mg., and by the fourth hour the blood sugar level was 59.8 mg. At no time was any sugar detected in the urine. By the time of discharge from the hospital the patient had gained 12¾ pounds (5.7 Kg.). She has continued in good physical condition, although to a certain extent there has been a recurrence of her mental condition.

Case 3.—J. C., a white man aged 56, was admitted to the hospital Sept. 3, 1939, with the chief complaints of depression, melancholia, anorexia and apprehension. His condition had come on gradually, dating back to April 1939, at which time he began to complain of gastrointestinal disturbances, loss of appetite, etc. The symptoms that he showed on admission had developed the preceding June. For a month prior to his admission he had eaten no solid food and had shown profound depression. Examination showed him to be well developed but emaciated. Other physical findings and the medical history were essentially of

no significance. The urine was normal, the nonprotein nitrogen was within normal limits and the fasting blood sugar was 75.3 per hundred cubic centimeters. A blood count, including a differential count, was within normal limits. The second day following admission a dextrose tolerance test was run. The resultant curve showed a fasting blood sugar of 73.3 mg. per hundred cubic centimeters. The blood sugar rose and reached its peak at the end of the first hour, at which time the reading was 235.3 mg. At the end of the second and the third hour it dropped to 161.3 and 51.7 mg., respectively. At the fourth hour it rose again to 129.0 mg. The patient's condition was diagnosed as an agitative depressive psychosis, and metrazol shock therapy was given. Intravenous injections of a 10 per cent solution of dextrose and vitamin B_1 (thiamine hydrochloride) also were given in the course of the treatment. The patient's psychosis cleared, and he was discharged from the hospital November 21, with a complete remission. Shortly prior to his discharge another dextrose tolerance test was run. The

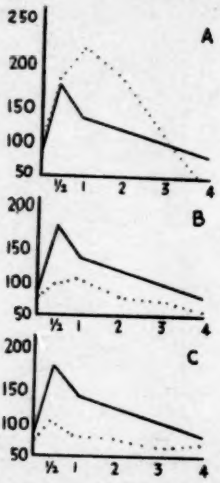

Fig. 4.—Dextrose tolerance curves for W. B. (case 4) obtained (*A*) Sept. 1, 1939, three days after admission to the hospital, (*B*) September 9, after eight days of treatment for alcoholism, and (*C*) September 19, after nineteen days of treatment for alcoholism.

fasting blood sugar was found to be 84.7 mg. per hundred cubic centimeters. At the end of one hour the level was 140.8 mg. It then dropped in the second and the third hour to 97.6 and 57.5 mg., respectively. At no time during this test was any sugar found in the urine.

Case 4.—W. B., a white man aged 37, was admitted to the hospital Aug. 29, 1939, in a state of profound physical exhaustion. The chief complaint was alcoholism. The onset of his condition had occurred insidiously several years earlier. He had eaten very little for some weeks prior to his admission. The dextrose tolerance test, along with other laboratory studies, was done on admission, and with the exception of the tolerance curve, all results were essentially irrelevant. The fasting level of the blood sugar, as indicated in figure 4 *A*, was 114.0 mg. per hundred cubic centimeters. At the end of one-half hour it had risen to 163.9

mg., and the one hour sample showed the peak of 227.3 mg. At the end of two hours the blood sugar level had dropped to 190.5 mg. and one hour later to 129.8 mg. The four hour sample showed the blood sugar to be 40.0 mg. Sugar in the urine reached its peak, a 3 plus reaction, at the first hourly interval, coincident with the high blood sugar level. This curve, according to all three criteria, is diabetic. This patient was treated for alcoholism, and in eight days another test was run. This time the curve was more nearly normal, with the following data: fasting level, 80.0 mg.; one-half hour, 103.1 mg.; two hours, 93 mg.; three hours, 81.6 mg., and four hours, 51.5 mg. The urine gave a negative reaction for sugar throughout the test. On September 19 another dextrose tolerance test was run, with the following results: fasting level, 80.0 mg.; one-half hour, 110.5 mg.; one hour, 88.9 mg.; two hours, 85.1 mg.; three hours, 69.1 mg., and four hours, 74.1 mg. The urine again gave a negative reaction for sugar. This curve, although low, is normal for this man. It is evident that he is not diabetic, but he could have been classified as such on admission by all three criteria. This patient, like those in cases 1, 2 and 3, showed this curve, we believe, because of pronounced malnutrition, in this case due to metabolic disturbances accompanying alcoholism.

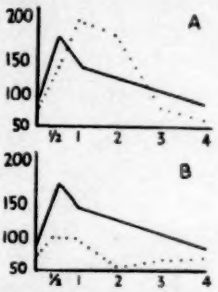

Fig. 5.—Dextrose tolerance curves for H. K. (case 5) obtained (*A*) Nov. 5, 1939, the day following admission to the hospital, and (*B*) November 19, after fourteen days of treatment for alcoholism.

Case 5.—H. K., a white man aged 44, was admitted to the hospital on Nov. 4, 1939, with the chief complaint of alcoholic toxemia. He was in a state of acute alcoholism on admission and was weak and malnourished. Physical examination revealed nothing else of importance. Laboratory examination of the blood and urine revealed nothing outstandingly abnormal except the dextrose tolerance. A tolerance test was run November 5, and the following results were obtained: fasting blood sugar, 70.4 mg.; one-half hour, 147.0 mg.; one hour, 200.0 mg.; two hours, 186.9 mg.; three hours, 80.0 mg., and four hours, 60.2 mg. Sugar in the urine at the beginning of the test was 0.5 mg. per hundred cubic centimeters. By the end of the second hour it was 5.75 mg., and it dropped by the third hour to 0.75 mg. Only a trace was found at the end of the fourth hour. The dextrose tolerance test was repeated November 18, with the following results: fasting blood sugar, 78.1 mg.; one-half hour, 109.9 mg.; one hour, 108.1 mg.; two hours, 45.5 mg.; three hours, 60.0 mg., and four hours, 66.7 mg. This curve is within normal limits; no sugar was found in the urine at any time.

In these 5 cases the only common denominator is malnutrition. In order to illustrate this point further, the cases of 2 patients with similar

chief complaints but with normal dextrose tolerance curves were selected for analysis.

CASE 6.—G. G., a white woman aged 39, was admitted to the hospital Oct. 10, 1939, with the chief complaint of alcoholism. The onset of her condition occurred about three years earlier, after a motor car accident in which a person was killed. At that time she began to drink excessively and continuously. On physical examination at the time of admission she appeared well nourished, although acutely intoxicated. Results of laboratory studies, including the dextrose tolerance test, were essentially normal. The following results were obtained from the tolerance test: fasting blood sugar, 71.9 mg.; one-half hour, 140.8 mg.; one hour, 72.6 mg.; two hours, 66.4 mg.; three hours, 89.3 mg., and four hours, 88.9 mg.

We present this case for comparison with cases 4 and 5, in both of which alcoholism was the chief complaint. We wish to stress that in cases 4 and 5 the tolerance curve was diabetic but in case 6 there was no disturbance of the tolerance curve, despite the patient's condition of chronic alcoholism. In all 3 of these cases the patients were, and had

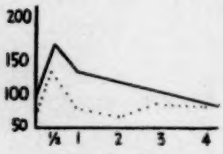

Figure 6

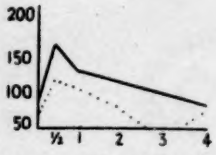

Figure 7

Fig. 6.—Dextrose tolerance curve for G. G. (case 6) obtained Oct. 11, 1939, the day following admission to the hospital.

Fig. 7.—Dextrose tolerance curve for G. Gen. (case 7).

been for some time, acutely intoxicated. All presented similar histories with only one variable—nutrition. The patient in case 6 had by proper diet kept her metabolic processes normal throughout her drinking episodes, while the other 2 had not and hence were suffering from malnutrition.

CASE 7.—G. Gen., a white man aged 54, was admitted to the hospital Sept. 18, 1939, in a state of hypomania, the onset of which occurred only a short time prior to admission. After a period of most severe physical and emotional stress, a typical manic psychosis had developed. Physical examination revealed a state of average nutrition but no pathologic condition or gross physical defects. Results of laboratory tests were essentially without significance, and the following tolerance curve, which is nondiabetic in character, was obtained: fasting blood sugar, 75.5 mg.; one-half hour, 129.0 mg.; one hour, 121.2 mg.; two hours, 93.0 mg.; three hours, 44.1 mg., and four hours, 66.6 mg.

The results in this case, and in several similar ones in our files, show that there is apparently no constant relation between manic-depressive episodes and a high dextrose tolerance curve. Diethelm,[5] Wittkower,[6]

5. Diethelm, O.: The Influence of Emotions on Dextrose Tolerance, Arch. Neurol. & Psychiat. **32**:342 (Aug.) 1936.

(Footnotes continued on next page)

McGowan[7] and Tod[8] have reported on disturbed dextrose tolerance curves associated with certain abnormal emotional states and with various psychotic reactions. They concluded that the disturbance of the dextrose tolerance curve was the result of the mental condition affecting bodily functions and reactions, that it had no etiologic significance and that it indicated an abnormal utilization of dextrose. Our observations do not seem to confirm their conclusions. Some of our most disturbed patients have a normal tolerance for dextrose, while many of our apparently calm patients, who give a history of malnutrition, have a poor tolerance, i. e., a diabetic-like curve.

COMMENT

We have analyzed these 7 cases to show that a diagnosis of clinical malnutrition can be confirmed with the help of the dextrose tolerance test. Frank disorders of metabolism and nutrition are, of course, obvious, but cases of marginal or developing malnutrition present no outstanding objective clinical signs, and it seems to us that the test in this respect should be valuable to the physician in general practice.

In our first 5 cases there was no question as to the presence of malnutrition, and in the last 2 there was no evidence of any kind in the history or examination of malnutrition or metabolic change. Between these two extremes there are, in our 200 cases, conditions representing all the stages of developing malnutrition, up to and including pellagra and beriberi. The two extreme conditions should be easy to interpret and diagnose. However, both in psychiatric and in general practice there are many cases in which there is a history of easy fatigue and other symptoms of malnutrition that make determination of the state of nutrition an important factor. It is in these cases that we have found this test and its interpretation of greatest importance. When we first began to determine tolerance curves routinely, we were greatly surprised at the findings, for it soon became evident that the most disturbed tolerance curves occurred in the cases of the most profound malnutrition. We could find no other common denominator. This interpretation was confirmed by the return of these curves to normal after therapy was directed at the malnutrition. The state of the psychosis had no effect on the curves. In some cases psychiatric recovery ensued without a return of normal metabolism; in others the curves returned to normal while the psychosis was still as active as at the time of admission.

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6. Wittkower, E.: The Influence of Emotions on Somatic Functions, J. Ment. Sc. **81**:533 (July) 1935.

7. McGowan, P. K.: Manic-Depressive Psychosis-Symposium: Hyperglycemic Index as Aid in Prognosis, J. Ment. Sc. **82**:589 (Sept.) 1936.

8. Tod, H.: Studies in Carbohydrate Metabolism in Mental Disorders, Edinburgh M. J. **43**:524 (Aug.) 1936.

When we analyzed the cases in the intermediate group, in which the history of malnutrition was indefinite or absent, we found that some of the curves were normal, while others were diabetic. The response of the curves to therapy was the same as in the cases of profound malnutrition. The only possible conclusion in the absence of some additional factor or evidence not yet apparent is that in those cases in which an indeterminate history was associated with a disturbed curve malnutrition was present. In some cases careful questioning brought out the story of an inadequate or improper diet, although the patient or his family had thought the diet suitable.

We consider that the dextrose tolerance test is a satisfactory test for the state of nutrition, as well as for diabetes mellitus, and believe that in cases in which the situation might indicate malnutrition, a dextrose tolerance test should be done and interpretations made from the standpoint of possible nutritional deficit, as well as from the standpoint of diabetes.

In 5 cases in which there were a typical history of malnutrition and physical evidence of long-standing improper metabolism we have shown that the dextrose tolerance curve was diabetic and that a diagnosis of diabetes mellitus could have been made at the time of admission. We have also shown that when proper nutrition was reestablished the tolerance curve returned to normal and remained so, without subsequent treatment of any kind other than a full diet. We have also presented 2 cases, of the same clinical type as some in which there were abnormal curves, in which a history of a full diet and absence of any metabolic change up to the time of admission were associated with normal curves.

These are selected cases, chosen because of the specificity of the findings. Our total group of cases in which tolerance tests were made has now reached approximately 200, as compared with that of 69 originally reported, and we find that this common denominator (malnutrition) runs throughout. In all cases in which the curves were not truly or frankly diabetic, the curve returned to normal within one to three months of the time that adequate nutrition was started.

Bowman, Wortis, Orenstein and Goldfarb [9] made a study of dextrose tolerance in a group of 18 patients with alcoholism. They reported:

> On admission there was a marked diminution of the sugar tolerance, which improved after one week in the hospital on a normal diet. It is suggested that the diminished tolerance was due to an undernourished state previous to admission.

Chambers [10] outlined the physiologic generalizations behind the concept of clinical marginal malnutrition as it affects the factors controlling

9. Bowman, K. M.; Wortis, J.; Orenstein, L., and Goldfarb, W.: The Sugar Tolerance of Alcoholic Patients, Proc. Soc. Exper. Biol. & Med. **42**:37 (Oct.) 1939.

10. Chambers, W. H.: Undernutrition and Carbohydrate Metabolism, Physiol. Rev. **18**:248 (April) 1938.

carbohydrate metabolism and the dextrose tolerance of the patient. We quote the opening paragraphs of his recent review.

Undernutrition is used in a broad sense in this paper to include complete inanition as well as the dietary deficiencies. Fasting has been recognized as a factor in carbohydrate metabolism since 1873, but the greatest expansion of the entire field has occurred in the past 15 years. During this time the endocrine control of carbohydrate metabolism has been developed and now occupies a position of major importance. An attempt to correlate the studies of undernutrition and the endocrine research has led to the following generalizations concerning carbohydrate utilization.

The maximum utilization of administered glucose is found in the normal individual when carbohydrate has been abundantly supplied in the diet. The minimum effect is obtained in the completely depancreatized animal which excretes all of the ingested sugar in the urine. Between these extremes is a series of less sharply defined intermediate stages. As the amount of carbohydrate in the diet is diminished the glucose tolerance test indicates a decreased utilization. During complete inanition there is a progressive deprivation of the carbohydrate stores in the body and an increasingly larger fraction of the test meal is lost by excretion as the fast continues. A more drastic and exaggerated condition is seen in the animal depleted by phlorhizin glycosuria. Approaching pancreatic diabetes at the lower end of the scale are the various stages of diabetes mellitus and the endocrine disturbances involving the pituitary and the adrenal. Of the many factors exerting a controlling influence on the different degrees of carbohydrate utilization as outlined, the importance of two is apparent—the amount of carbohydrate available to the cells and the endocrine control. The former seems to predominate at the beginning of the series but is superseded by the latter toward the minimum end. The literature presented in this review will give the evidence supporting these generalizations, with particular emphasis on the nutritional condition with respect to carbohydrate.

The conception of carbohydrate metabolism outlined above is based on the measurement of the body's ability to utilize carbohydrate, as determined by its reactions for several hours after the administration of pure glucose. When a glucose test meal is ingested sufficient in amount to maintain the maximum rate of absorption from the intestines for several hours, the total heat production of the body indicates that in the normal well-fed organism only about one-quarter to one-third of the absorbed sugar can be oxidized to CO_2 and H_2O. The major portion of the remainder is probably stored as glycogen, but conversion into fat, glycolysis to lactic acid, transformation into hexosephosphate, glycerophosphate, glucosamine, or other compounds may occur. These reactions may be observed in several ways. The method most extensively used for the study of carbohydrate metabolism has been the glucose tolerance test in which the rise and fall in blood sugar concentration are determined for several hours after the administration of sugar. This test is most useful in showing small differences in utilization. It should be remembered that the blood sugar changes reflect the rate but not the nature of glucose utilization. If the impairment is large enough, information as to the total amount utilized may be obtained from the quantitative collection of the fraction excreted by the kidney. The most direct evidence for oxidation comes from carefully conducted determinations of the respiratory metabolism sufficient in duration to yield combustion quotients when interfering changes in the body are adequately controlled (Richardson, 1929). Tissue analyses yield data concerning glycogen deposition and other methods of disposal. All of these reactions must be considered in establishing a complete picture of carbohydrate

utilization. The terms "utilization" and "oxidation" have been used synonymously in some of the recent literature. This is obviously inexact in short experiments.

We believe that a diagnosis of diabetes mellitus should not be made until the possibility of malnutrition has been eliminated by maintaining over a rather long period a full diet, supplemented by vitamins of the B complex and insulin in small doses (5 to 10 units), in order to revitalize the mechanisms of carbohydrate metabolism. If the curve returns to normal and remains normal for one month while the patient is taking a full diet but no insulin, then the diagnosis of malnutrition has been confirmed. If, however, the curve does not return to normal during a three month trial period or becomes abnormal again when the insulin is stopped but a full diet maintained, then a diagnosis of diabetes must be considered as the probable interpretation of the tolerance disturbance.

Millions of dollars are being spent annually on vitamins. We feel that much of this is wasted because administration of vitamins as a deficiency therapy is indicated only when malnutrition is present. If there is no malnutrition, synthetic or extracted vitamins are not needed. The members of the vitamin B complex are given indiscriminately in cases of alcoholism, nervous disturbance, mild psychosis, etc.; yet in many cases of such conditions there is no malnutrition and, therefore, no need for vitamin therapy.

We believe that whenever the presence of malnutrition is suspected, a dextrose tolerance test should be done. The results will usually confirm or deny the diagnosis. When an abnormal tolerance curve is present, malnutrition should be diagnosed and treated; when such a curve is not present, nutritional therapy is not indicated. As a result of these studies we wish to reaffirm our previous statement that the diagnosis of diabetes should be approached with caution when the diagnosis of malnutrition is a possible alternative.

CONCLUSIONS

1. Malnutrition disturbs the dextrose tolerance of the patient and produces a clinical condition which might be called pseudodiabetes.

2. Early developing or marginal malnutrition should be considered as a possible diagnosis whenever the dextrose tolerance curve is diabetic-like.

3. The nervous or psychotic patient should be relieved of his malnutrition by appropriate means before intensive therapy of other types is started, but it is not necessary to wait for the tolerance curve to return to normal before the other measures are instituted.

4. A diagnosis of diabetes mellitus should not be made until an appropriate period of treatment with a full diet has passed without the return of the dextrose tolerance curve to normal.

2625 Paseo.

ACUTE, MASSIVE HEMOGLOBINURIA OF OBSCURE CAUSE, WITH JAUNDICE AND ANEMIA

REPORT OF A CASE WITH CLINICAL AND HEMATOLOGIC STUDIES AND MEASUREMENTS OF THE BLOOD PIGMENT METABOLISM

MARK D. ALTSCHULE, M.D.
AND
D. ROURKE GILLIGAN, M.S.
BOSTON

Hemoglobinuria is encountered in several well defined clinical conditions in which intravascular hemolysis occurs. In the present study an unusual case of acute, severe hemoglobinuria, accompanied by jaundice and slowly developing anemia, with final recovery, is reported.

The clinical and laboratory findings in this case do not conform completely with those in any recognized type of hemolytic attack leading to hemoglobinuria. The diagnostic procedures utilized are discussed. The effects of posture and of exercise on the production of hemolysis were investigated.

The continuation of the hemolytic attack for three weeks in this case gave an unusual opportunity for studying the quantitative aspects of the hemolysis. Hematologic studies were made; the plasma and the urine hemoglobin and the plasma bilirubin were studied quantitatively, and the urinary and fecal excretions of urobilinogen were measured. The total amount and rate of hemolysis during the attack have been calculated from certain of these data.

METHODS OF INVESTIGATION

The hematologic and chemical methods employed have been outlined in some detail in previous articles.[1] Briefly, they were as follows: The method of Evelyn [2]

From the Medical Service and Medical Research Laboratories, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School.

1. (*a*) Gilligan, D. R.; Altschule, M. D., and Katersky, E. M.: Studies of Hemoglobinemia and Hemoglobinuria Produced in Man by Intravenous Injection of Hemoglobin Solutions, J. Clin. Investigation **20**:177, 1941. (*b*) Gilligan, D. R., and Blumgart, H. L.: March Hemoglobinuria: Studies of the Clinical Characteristics and Mechanism, with Observations in Three New Cases, and Review of the Literature, Medicine **20**:34, 1941.

2. Evelyn, K. A.: A Stabilized Photoelectric Colorimeter with Light Filters, J. Biol. Chem. **115**:63, 1936.

was used in measuring blood hemoglobin; reticulocytes and platelets were counted in wet preparations according to Dameshek;[3] hematocrit values were measured on samples of blood, with oxalate mixture as anticoagulant,[4] in Rourke-Ernstene sedimentation tubes;[5] the resistance of the red blood cells to hypotonic solutions of soduim chloride was measured according to Daland and Worthley;[6] the lysolecithin fragility test was made by the method of Singer;[7] plasma bilirubin was measured by the method of Malloy and Evelyn[8] (as described previously,[1a] the bilirubin values obtained by this method are appreciably lower than the actual values when the plasma contains hemoglobin in concentrations over 30 mg. per hundred cubic centimeters); the plasma and urine hemoglobin values were measured as described by Bing and Baker,[9] with modifications outlined in a previous article;[1a] the total protein of the urine was measured gravometrically after precipitation with trichloroacetic acid;[1a] the urea clearance was measured according to Van Slyke, Page, Hiller and Kirk;[10] urobilinogen in the urine and the stool was measured according to Watson;[11] the Donath-Landsteiner test was conducted according to Mackenzie[12] (guinea pig complement was added), and the acid hemolysis test for diagnosis of the paroxysmal nocturnal type of hemoglobinuria was made according to Ham.[13] Hemoglobin pigments in the blood and urine were identified by spectroscopic and spectrophotometric examination. The same precautions were exercised here as in previous work to prevent extravascular hemolysis during

3. Dameshek, W.: A Method for the Simultaneous Enumeration of the Blood Platelets and Reticulocytes, with Consideration of the Normal Blood Platelet Count in Men and in Women, Arch. Int. Med. **50**:579 (Oct.) 1932.

4. Heller, V. G., and Paul, H.: Changes in Cell Volume Produced by Varying Concentrations of Different Anticoagulants, J. Lab. & Clin. Med. **19**:777, 1934.

5. Rourke, M. D., and Ernstene, A. C.: A Method for Correcting the Erythrocyte Sedimentation Rate for Variations in the Cell Volume Percentage of Blood, J. Clin. Investigation **8**:545, 1930.

6. Daland, G. A., and Worthley, K.: The Resistance of Red Blood Cells to Hemolysis in Hypotonic Solutions of Sodium Chloride: Observations in Blood Disorders, J. Lab. & Clin. Med. **20**:1122, 1935.

7. Singer, K.: The Lysolecithin Fragility Test, Am. J. M. Sc. **199**:466, 1940.

8. Malloy, H. T., and Evelyn, K. A.: The Determination of Bilirubin with the Photoelectric Colorimeter, J. Biol. Chem. **119**:481, 1937.

9. Bing, F. C., and Baker, R. W.: Determination of Hemoglobin in Minute Amounts of Blood by Wu's Method, J. Biol. Chem. **92**:589, 1931. Bing, F. C.: Purification of Benzidine, and an Improved Reagent, for Estimating Hemoglobin in Blood, ibid. **95**:387, 1932.

10. Van Slyke, D. D.; Page, I. H.; Hiller, A., and Kirk, E.: Studies of Urea Excretion: IX. Comparison of Urea Clearances Calculated from the Excretion of Urea, of Urea Plus Ammonia, and of Nitrogen Determinable by Hypobromite, J. Clin. Investigation **14**:901, 1935.

11. Watson, C. J.: Studies of Urobilinogen: I. An Improved Method for the Quantitative Estimation of Urobilinogen in Urine and Feces, Am. J. Clin. Path. **6**: 458, 1936.

12. Mackenzie, G. M.: Paroxysmal Hemoglobinuria, Medicine **8**:159, 1929.

13. Ham, T. H.: Studies on Destruction of Red Blood Cells: I. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria; an Investigation of the Mechanism of Hemolysis, with Observations on Five Cases, Arch. Int. Med. **64**:1271 (Dec.) 1939.

the drawing and handling of the samples of blood.[13] The blood volume was calculated from data given by Gibson and Evans,[14] which correlate the blood volume of normal persons with the surface area.

REPORT OF CASE

J. Y., a 77 year old Russian-Jewish retired barber, was admitted to the genito-urinary service of the Beth Israel Hospital on April 21, 1940 because he had passed several specimens of "black" urine during the previous twenty-four hours. The family history was irrelevant. The patient had had typhus fever, characterized by high temperature, severe headache and "spots all over the body," when in Europe during the Russo-Turkish War, in 1877. After this he was entirely well until 1930, when a right inguinal hernia developed, which was operated on at this hospital a year later. In 1936 a strangulated right femoral hernia and in 1939 an incarcerated left femoral hernia were operated on. In 1937 he received treatment in the outpatient department for hypertrophic arthritis, which had begun to cause symptoms a year earlier. On several examinations, in the period between 1931 and 1939, he was found to have a blood pressure of approximately 160 systolic and 90 diastolic, cardiac enlargement with an apical systolic murmur, pulmonary emphysema, a few rales over the base of the left lung, peripheral arteriosclerosis, varicose veins in the legs and an epigastric hernia. There was no enlargement of the liver or the spleen. Occasionally he experienced slight burning on urination. Several examinations between 1931 and 1937 revealed a red blood cell count of approximately 4,900,000 per cubic millimeter; normal urine, with specific gravity as high as 1.025; normal blood nonprotein nitrgoen values and negative reactions to the Wassermann, Hinton and Kahn tests. In 1939 his urine contained small amounts of albumin and occasional leukocytes and erythrocytes and had a specific gravity of 1.020. Shortly thereafter, about four months before his present admission, he noted nocturia, with micturition twice a night. Beginning in 1936, he showed gradual loss in weight, amounting to 30 pounds (13.6 Kg.) in four years. He had taken no medication at any time during his life, except during his various periods of hospitalization, and had never been exposed to noxious chemicals.

On April 20, after sitting in a cinema for three hours, the patient voided "black" urine. During the night he voided eight or nine times, passing "black" urine each time and experiencing slight burning on urination. Between 7 a. m. and 12 noon of the next day he experienced considerable urgency but was unable to void. He was admitted to the hospital at noon and passed 14 ounces (414 cc.) of dark burgundy red urine shortly after admission; there were no further indications of suppression of the urinary flow. Physical examination gave information as previously noted, with the addition of slight icterus, enlargement of the liver to 4 cm. below the costal margin and a barely palpable spleen. The body temperature was 99.5 F. (rectal).

14. Gibson, J. G., II, and Evans, W. A., Jr.: Clinical Studies of the Blood Volume: II. The Relation of Plasma and Total Blood Volume to Venous Pressure, Blood Velocity Rate, Physical Measurements, Age and Sex in Ninety Normal Humans, J. Clin. Investigation **16**:317, 1937.

Examination of the urinary sediment revealed only rare red blood cells and a few white blood cells. After centrifugation the urine gave strongly positive reactions to the guaiac and benzidine tests. The specific gravity was 1.007 and the reaction slightly alkaline. The nitric acid test showed a large amount of "albumin." The plasma was dark red and gave a strongly positive benzidine reaction.

Hematologic examination on the following morning (April 22) showed a red blood cell count of 4,710,000 per cubic millimeter, a hemoglobin concentration of 94 per cent (Evelyn) and a white blood cell count of 10,000 per cubic millimeter, with 67 per cent polymorphonuclear leukocytes, 23 per cent lymphocytes and 10 per cent monocytes. The fragility of the red blood cells to hypotonic solutions of sodium chloride was normal. At this time the blood nonprotein nitrogen was 90 mg. per hundred cubic centimeters, and on the following day it was 78 mg. per hundred cubic centimeters, with a value for blood urea nitrogen of 44 mg. per hundred cubic centimeters. The urea clearance was 20 per cent of normal.

The clinical diagnosis on admission was hemoglobinemia, hemoglobinuria, icterus, hypertension, generalized arteriosclerosis, hypertensive heart disease, cardiac enlargement, chronic nephritis, pulmonary emphysema, varicose veins and epigastric hernia.

The patient was given a house diet and 3,600 cc. of fluids daily. Five grams of sodium bicarbonate was administered orally six times daily; this medication was reduced to 4 Gm. daily on April 25 and was discontinued on May 2. The urine was burgundy red for the first three days after admission, and hemoglobin did not completely disappear from the urine until about three weeks later (figure). The icterus increased during the first four days after admission, became moderately intense and disappeared during the next week. Because of the development of moderate anemia, administration of exsiccated ferrous sulfate, 0.2 Gm. four times daily, was started on May 8 and continued until July 10. Nocturia, with micturition three or four times a night, persisted throughout the patient's stay in the hospital. The stools were all of normal color. On the third and fourth days of the attack the stool showed a 4 plus guaiac reaction; several subsequent examinations of stools at intervals during the following months showed negative guaiac reactions.

The patient vomited on the day of admission. During the first three days of his stay in the hospital he experienced mild anorexia and heartburn and some constipation, cramps and distention, relieved by enemas; these disturbances did not recur. There was slight burning on urination at various times. The patient otherwise felt well, except for weakness and mild dyspnea on exertion a week after admission, when he was first allowed out of bed. The body temperature was not elevated at any time.

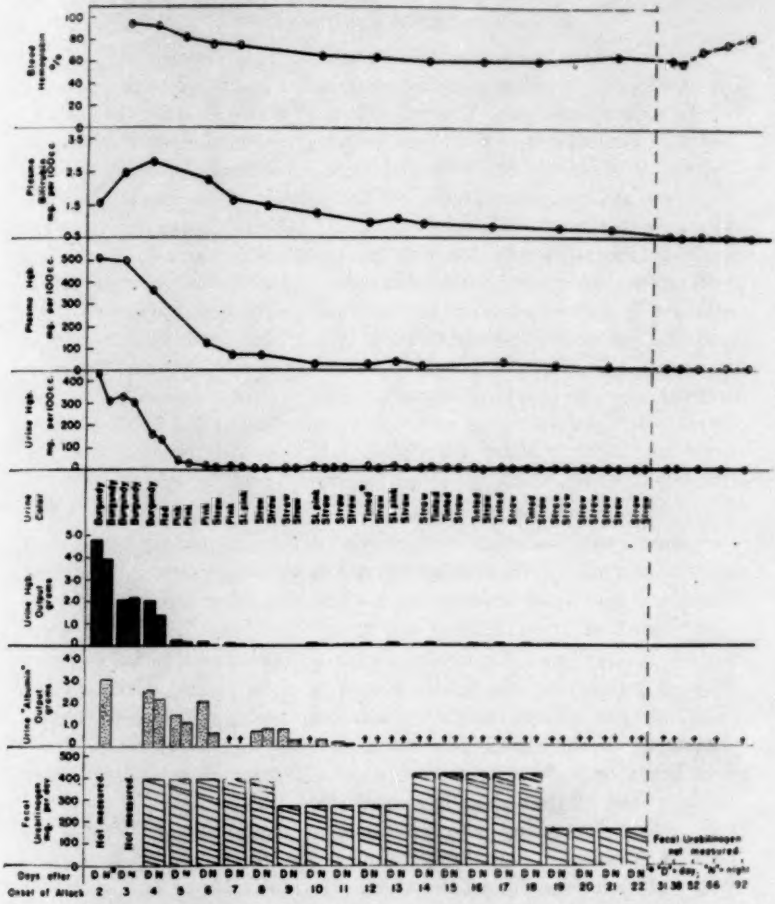
Roentgenographic studies on April 23 revealed the following conditions: hypertrophic arthritis of the spine; pulmonary emphysema, with several dense nodules in the right hilar region; marked calcification of the aorta and the splenic artery; a sharply defined area of increased radiance over the left half of the diaphragm, interpreted as due to a congenital cyst of the lung, and a globular right kidney. Barium sulfate studies of the gastrointestinal tract on April 24 showed nothing significant; enlargement of the liver and the spleen were noted.

The electrocardiogram was normal, except for left axis deviation.

At the time of discharge from the hospital the patient had nocturia, with the passage of urine three to four times a night. This persisted for approximately three months and then decreased to once a night. Simultaneously albuminuria, moderate at all times, became persistently minimal. The blood nonprotein nitrogen level, elevated to 60 mg. per hundred cubic centimeters at the time of discharge

from the hospital, was normal two months later; the urea clearance was 99 per cent of normal five months after discharge.

Dyspnea recurred several months after discharge from the hospital but was relieved by digitalization. The liver remained palpable, but the spleen could not be felt after discharge, although roentgen examination showed it to be still enlarged.


Blood Hemoglobin %
Plasma Bilirubin mg. per 100 c.c.
Plasma Hgb. mg. per 100 c.c.
Urine Hgb. mg. per 100 c.c.
Urine Color
Urine Hgb. Output grams
Urine "Albumin" Output grams
Fecal Urobilinogen mg. per day
Not measured.
Not measured
Fecal Urobilinogen not measured
Days after Onset of Attack

Metabolism of hemoglobin during the attack of hemoglobinuria and during recovery. Note the greater excretion of hemoglobin in the urine when the patient was up and about during the seventh to the eighteenth day of the attack. The values for concentration of bilirubin in the plasma during the period when the concentration of hemoglobin in the plasma was above 30 mg. per hundred cubic centimeters are probably appreciably less than the actual amounts. Such discrepancy is discussed in the section on methods.

The patient reported that two months after the first episode of hemoglobinuria he passed bright red urine in the evening after a banquet and that he voided two progressively paler urines during the night and one at 6 a. m. which appeared normal in color. Since none of these urines were submitted to us for examination, it is impossible to evaluate the patient's observations.

OBSERVATIONS AND COMMENT

Hematologic Observations.—Hematologic studies made on the second day of illness, i. e., after two days of massive hemoglobinuria, revealed normal values (table 1). The red cell count was 4,710,000, the concentration of hemoglobin in the blood 94 per cent and the white cell count 10,100. With continuing hemoglobinemia and hemoglobinuria the red cell count and the concentration of hemoglobin in the blood gradually decreased to their lowest values of 2,920,000 and 59 per cent, respectively, on the fourteenth day after the onset of the attack. There was moderate reticulocytosis during this period. During the following week, when the hemoglobinemia and hemoglobinuria gradually disappeared, the red cell count and the concentration of hemoglobin in the blood increased somewhat, being 3,780,000 and 66 per cent, respectively, on the twenty-first day after the onset of the attack. The moderate reticulocytosis continued. The platelet count, white blood cell count and differential count were normal throughout the illness. Within two months after the termination of the attack the blood picture returned to normal (table 1).

Differential Diagnostic Studies.—This case of acute, severe hemoglobinuria, with jaundice and slowly developing anemia, occurring initially in a man aged 77, presented a difficult diagnostic problem. The attack was essentially asymptomatic. The slight burning on micturition experienced at times during the attack had also been experienced earlier and persisted during the follow-up period; nocturia was more frequent during the attack than before or after. There were no chills, fever, muscle pains, malaise, prostration or allergic manifestations. The onset of the attack was not associated with ingestion of drugs, fava beans or mushrooms; there was no history of exposure to toxic gases. Tests on the sixth and seventh days after the onset of the hemolytic attack showed no autoagglutinins on incubation of serum in the cold or at body or room temperature. The fragility of the red blood cells to hypotonic solutions of sodium chloride (table 1) and to lysolecithin was normal. The size and shape of the red blood cells appeared normal.

The clinical and laboratory findings in this case were compared with those in cases of recognized syndromes leading to hemoglobinuria in an attempt to make a differential diagnosis.

The history and findings ruled out hemoglobinuria due to infection, massive intraperitoneal hemorrhage and ingestion or inhalation of toxic substances.

TABLE 1.—*Hematologic Data During and After the Attack of Hemoglobinuria*

Date 1940		Day After Onset of Hemoglobinuria	Red Blood Cell Count, per Cu. Mm.	Blood Hemoglobin, Percentage	Hematocrit Reading, Percentage of Cells	Reticulocytes, Percentage	Platelets, per Cu. Mm.	White Blood Cell Count, per Cu. Mm.	Fragility to Hypotonic Solutions of Sodium Chloride	
									Minimum Resistance, Percentage of Sodium Chloride	Maximum Resistance, Percentage of Sodium Chloride
					During Attack					
4/22	.....	3	4,710,000	94	44.0	...	.....	10,100	44-40	26-24
4/23	.....	4	4,690,000	91	....	2.3	400,000	10,300	.....	.....
4/24	.....	5	4,220,000	81	....	1.8	.....	8,700	.....	.....
4/25	.....	6	4,080,000	76	....	2.4	.....	7,000	46-40	26-24
4/26	.....	7	3,710,000	73	34.8	...	.....	5,500		
4/29	.....	10	3,720,000	64	....	2.1	531,000	5,100		
5/ 1	.....	12	3,320,000	63	....	...	.....	.....		
5/ 3	.....	14	2,920,000	59	28.5	...	.....	4,200		
5/ 5	.....	16	3,000,000	60	....	...	.....	.....		
5/ 7	.....	18	3,180,000	60	....	3.4	693,000	5,400		
5/10 *	.....	21	3,780,000	66	....	1.4	560,000	7,200		
					Follow-Up Period					
5/20	.....	..	3,540,000	63	29.3	2.7	380,000	7,400		
6/10	.....	..	3,530,000	71	34.0	0.1	183,000	6,400		
6/24	.....	..	4,500,000	77	37.5	...	.....	7,200		
7/10	.....	..	4,290,000	86	....	1.8	335,000	6,800		
10/30	.....	..	5,020,000	91	43.9					

* End of attack.

That the pigmentation of the plasma and the urine was due to hemoglobin, and not to myoglobin, was established by spectrophotometric studies.[15] Examinations of the plasma and the urine on the third day of illness revealed in each a point of maximum absorption at 575 millimicrons. This value agrees closely with the reported alpha band for human oxyhemoglobin,[16] whereas the alpha band for oxymyoglobin is 581 millimicrons.[17] Another point of maximum absorption was found in the plasma, and more faintly in the urine, at 619 millimicrons. This band shows the presence of methemalbumin, and its significance is discussed later. The clinical features of the attack in this case did not correspond in any way to those in an attack of myoglobinuria, which condition is characterized by muscle pains and stiffness, paralysis and extreme prostration and frequently terminates fatally.[18]

The findings did not correspond with those in attacks of paroxysmal hemoglobinuria of the chill or syphilitic type.[12] Reactions to Wassermann, Hinton and Kahn tests were negative. The Donath-Landsteiner test for cold hemolysins was negative on two examinations. Besides these negative laboratory data, the absence of symptoms and the long duration of the attack were further important criteria which ruled out the diagnosis of paroxysmal hemoglobinuria of the syphilitic type.

The diagnosis of chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria (Marchiafava-Micheli disease)[19] was excluded. An important criterion of this syndrome, as implied by the name, is marked exacerbation of hemolysis during sleep. In our patient the degree of hemoglobinuria was not greater during sleep than during waking hours (figure). Hemosiderinuria, which occurs constantly in cases of Marchiafava-Micheli disease,[19] was not observed. The acid hemolysis test, diagnostic of Marchiafava-Micheli disease,[13] gave negative results on repeated occasions. The absence of anemia and of jaundice prior to the onset of massive hemoglobinuria, the cessation of hemolysis after three weeks and the advanced age of the patient further ruled out Marchiafava-Micheli disease.

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15. The spectrophotometric studies reported here were made by Dr. John F. Taylor, of the Biochemistry Department, Harvard Medical School. A Köning-Martens type of spectrophotometer was used.

16. Anson, M. L.; Barcroft, J.; Mirsky, A. E., and Oinuma, S.: On the Correlation Between the Spectra of Various Haemoglobins and Their Relative Affinities for Oxygen and Carbon Monoxide, Proc. Roy. Soc., London, s.B **97**:61, 1924.

17. Millikan, G. A.: Muscle Hemoglobin, Physiol. Rev. **19**:503, 1939.

18. (*a*) Hamburger, L. P., and Bernstein, A.: Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria, Am. J. M. Sc. **192**:301, 1936. (*b*) Millikan.[17]

19. Ham.[13] Hamburger and Bernstein.[18a]

Hemoglobinuria is observed not infrequently in cases of acute hemolytic anemia of the so-called Lederer type.[20] This condition occurs usually in children and in young adults; the hemolytic crisis is heralded by fever, vomiting, abdominal pain, somnolence and restlessness; the hemolysis results in severe anemia and jaundice, and there is usually marked leukocytosis. The advanced age of the patient in our case, the asymptomatic onset of the attack, the absence of fever and leukocytosis and the slow development of only moderate anemia are in contrast to the clinical picture in cases of typical acute hemolytic anemia of the Lederer type.

Hemoglobinuria rarely occurs in cases of chronic hemolytic jaundice.[21] The clinical and laboratory data clearly preclude this diagnosis.

The findings in this case differed importantly from those in cases of march hemoglobinuria, in which condition paroxysmal attacks of hemoglobinuria occur in young men after short walks, long army pack marches or long strenuous runs.[1b] Attacks may be repeatedly initiated over a period of a few years by a given exertion, or the condition may disappear completely after a few months. The paroxysms are usually unassociated with any symptoms. Hemoglobinuria usually lasts for only a few hours; in 1 unusual case the hemoglobinuria sometimes lasted for two or three days.[22] Hematologic studies do not reveal anemia, reticulocytosis or any other abnormality. Physical examination in most instances yields nothing significant. After attacks the plasma bilirubin increases somewhat but not sufficiently to cause clinical icterus. The advanced age of our patient and the long duration of the attack of hemoglobinemia and hemoglobinuria, with development of moderate anemia and jaundice, were features markedly dissimilar to those in cases of march hemoglobinuria. Further, although hemolysis during the attack appeared to be exacerbated in this patient by exercise, as discussed later, no hemolytic attack could be initiated by having the patient walk considerable distances.

Bittorf [23] has reported several instances of hemoglobinuria occurring during attacks of acute glomerulonephritis. He found no hemoglobin in the plasma during the height of the hemoglobinuria in any of his patients. The patient whose condition is discussed here clearly did not fall into a group with these others.

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20. Dameshek, W., and Schwartz, S. O.: Acute Hemolytic Anemia (Acquired Hemolytic Icterus, Acute Type), Medicine **19**:231, 1940.

21. Batschwaroff, W.: Hämoglobinurie bei Icterus haemolyticus, Deutsche med. Wchnschr. **64**:191, 1938.

22. Foerster, A.: Ueber Marschhämoglobinurie, München. med. Wchnschr. **66**:554, 1919.

23. Bittorf, A.: Hämoglobinurische Nachschübe bei abklingender akuter hämorrhagischer Glomerulonephritis, München. med. Wchnschr. **68**:807, 1921.

The etiologic mechanism responsible for the hemolysis in this case was not suggested by any of the clinical or laboratory findings. The presence of occult blood in the stool during the height of the hemolytic attack was not considered due to a lesion of the gastrointestinal tract, but rather was ascribed to passage of hemoglobin from the plasma to the lumen of the bowel; a positive reaction for occult blood in the stool of a young adult patient with hemoglobinuria due to favism has been reported.[24] The persistence of the enlargement of the liver and the spleen during the six months of follow-up study since the disappearance of hemoglobinemia suggests that enlargement of these organs was not due entirely to the hemolytic attack. No diagnosis which would explain the enlargement of these organs could be established; it was felt, however, that cirrhosis of the liver was a possibility.

Metabolism of Blood Pigment.—The urine voided after admission to the hospital, twenty-four hours after the onset of the attack of hemoglobinuria, was dark burgundy red and contained 740 mg. of dissolved hemoglobin per hundred cubic centimeters; the plasma was dark red and contained 510 mg. of hemoglobin per hundred cubic centimeters. The plasma bilirubin was 1.5 mg. per hundred cubic centimeters[25] (figure), and slight icterus was noted. During the first twenty-four hours after admission a total of 8.7 Gm. of hemoglobin was excreted in the urine (figure).

During the first seven days of the attack the plasma and urine remained red (figure), the color decreasing gradually in intensity. On the seventh day, the concentration of hemoglobin in the plasma was 72 mg. per hundred cubic centimeters and the total urinary excretion of hemoglobin was 0.27 Gm., as compared with 8.7 Gm. on the first day after admission. The plasma bilirubin increased to 2.8 mg. per hundred cubic centimeters on the fourth day of the attack and decreased to 1.6 mg. on the seventh day (figure); the van den Bergh reaction was always indirect. Changes in the degree of jaundice approximately paralleled the levels of bilirubin. By the seventh day the red blood cell count had decreased to 3,700,000 per cubic millimeter (table 1). Blood destruction was further demonstrated by the abnormally high fecal urobilinogen excretion during this period (figure).

From the eighth to the eighteenth day the plasma was reddish brown and the concentration of hemoglobin varied around 30 mg. per hundred cubic centimeters. The urine contained much less hemoglobin

24. Hutton, J. E.: Favism: An Unusually Observed Type of Hemolytic Anemia, J. A. M. A. **109**:1618 (Nov. 13) 1937.

25. As stated in the section on methods, the values for plasma bilirubin are somewhat lower than actual in the presence of hemoglobinemia.

than on the previous days, the daily output ranging from 0.0 to 0.11 Gm. (figure). The red blood cell count further decreased to 2,920,000 per cubic millimeter on the fourteenth day and remained at approximately this level for the next four days (table 1). By the eighteenth day the bilirubin in the plasma had decreased to 0.8 mg. per hundred cubic centimeters and jaundice had disappeared. The fecal urobilinogen excretion remained elevated (figure). In this period blood destruction, although less marked than during the first six days, still continued, as evidenced by the persistence of hemoglobinemia and hemoglobinuria, by the further fall in the red cell count and concentration of hemoglobin in the presence of mild reticulocytosis and by the increased fecal urobilinogen excretion.

During the nineteenth to the twenty-second day evidences of abnormal hemolysis disappeared. The plasma hemoglobin was 8 mg per hundred cubic centimeters on the twenty-second day, a value within normal limits. The urine was completely free of hemoglobin from the twentieth to the twenty-second day. The fecal output of urobilinogen had decreased from the highest value of 416 mg. per day to one of 159 mg. per day (figure). Blood production was evidenced by the rise in the red cell count to 3,780,000 per cubic millimeter on the twenty-first day, by the increase in hemoglobin concentration to 66 per cent and by continued reticulocytosis (table 1).

Quantitative Estimation of the Extent of Intravascular Hemolysis Based on the Values for Plasma Hemoglobin.—The question arises whether the degree of intravascular hemolysis as indicated by the hemoglobinemia and hemoglobinuria was sufficiently great to cause anemia, jaundice and increased urobilinogen excretion.

Available data allow estimation of the amount of blood destruction required to maintain a given degree of hemoglobinemia. Hemoglobin in the plasma is destroyed gradually by the reticuloendothelial system, and at high levels of plasma hemoglobin some is excreted in the urine.[26] The rate of disappearance of hemoglobin from the plasma at varying levels of plasma hemoglobin after single intravenous injections of hemoglobin in normal persons has been studied recently in this laboratory.[1a] The resultant data are applicable in ascertaining whether in a given patient with hemoglobinemia the hemoglobin is disappearing from the plasma at the rate expected if no more hemoglobin is being delivered to it or, if the hemolysis is continuing, the data allow estimation of the amount of hemoglobin which must be supplied to the

26. Ottenberg, R., and Fox, C. L., Jr.: The Rate of Removal of Hemoglobin from the Circulation and Its Renal Threshold in Human Beings, Am. J. Physiol. **123**:516, 1938. Gilligan, Altschule and Katersky.[1a]

plasma to maintain a given degree of hemoglobin.[27] Unfortunately, the rate of disappearance of hemoglobin at blood levels of 500 mg. per hundred cubic centimeters was not measured after injections of hemoglobin in normal persons because we observed temporary untoward reactions even when levels of 300 to 400 mg. per hundred cubic centimeters were induced.[28] However, extension of the curve for the rate of disappearance of hemoglobin at lower levels of hemoglobin indicated that the concentration of plasma hemoglobin would decrease at a rate of about 75 mg. per hundred cubic centimeters per hour at a plasma hemoglobin level of 500 mg. per hundred cubic centimeters. This value includes the hemoglobin broken into its derived pigments and the hemoglobin excreted in the urine.

Since in this case the plasma hemoglobin level did not change appreciably from the second to the third day of the attack, it can be estimated that hemoglobin was being delivered to the plasma as fast as it was disappearing, namely, about 75 mg. per hour for each hundred cubic centimeters. This would amount in twenty-four hours, with the patient's estimated plasma volume of 2,150 cc.,[29] to 38.7 Gm. of hemoglobin, or the hemoglobin equivalent of 265 cc. of the patient's blood, as determined by the formula $\frac{38.7}{14.6} \times 100$, (table 2). Judging from the patient's history of passing "black" urine for the first twenty-four hours after

27. A small error giving slightly higher than actual values for blood destruction may be present in applying the data for the rate of disappearance of plasma hemoglobin after single intravenous injections of plasma hemoglobin in normal subjects to the data in a case of more long-standing hemoglobinemia. This possible error is noted because it has been shown that methemalbumin, which occurs together with oxyhemoglobin in the plasma of patients with hemoglobinuria of several days' duration or longer and which was present in our patient's plasma, disappears from the circulation less rapidly than oxyhemoglobin (Fairley [33]).

From this same source a small error giving slightly lower than actual values for blood destruction may be present in calculations based on the fecal urobilinogen excretion, since available evidence indicates that methemalbumin is excreted by the liver, the prosthetic group probably appearing in the feces as a porphyrin (Rimington, C.: Porphyrins and Their Relation to the Metabolism of Blood Pigments, Proc. Roy. Soc. Med. **32**:1268, 1939).

28. Footnote 1a. Hemoglobin disappeared from the plasma at the average rate of 10 mg. per hundred cubic centimeters of plasma per hour at an average plasma hemoglobin level of 30 mg. per hundred cubic centimeters and at rates of 28 and 47 mg. per hundred cubic centimeters per hour at average plasma hemoglobin levels of 99 and 201 mg. per hundred cubic centimeters, respectively.

29. The plasma volume was estimated from the blood volume (calculated from the data of Gibson and Evans [14]) and from the patient's hematocrit value of 44 per cent. The plasma volume probably increased somewhat during the later periods, when the hematocrit reading was approximately 30 per cent; for purposes of simplicity the initial calculated plasma volume is used throughout these calculations.

the onset of the attack, i. e., before admission to the hospital, and from the observations on admission that the plasma bilirubin was already elevated and mild jaundice was present, we estimated that the blood destroyed during the first day of the attack was at least as much as that destroyed on the second day of the illness. On the third day after the beginning of the attack the plasma hemoglobin decreased to 360 mg. per hundred cubic centimeters, an indication that hemolysis was somewhat less severe and that the plasma hemoglobin was decreasing at a rate of 6 mg. per hour per hundred cubic centimeters of plasma. The average estimated amount of hemoglobin delivered to plasma for this day, calculated from the mean blood hemoglobin value between 500 and 360 mg., namely, 430 mg., according to the formula $\frac{68 \times 21.50 \times 24}{1,000}$, is 35.1 Gm., the equivalent of 244 cc. of blood of the blood hemoglobin level of the patient for the day. The fourth to the sixth day after the onset of the attack the level of the plasma hemoglobin decreased from 360 to 122 mg. per hundred cubic centimeters, an average rate of disappearance of 5 mg. per hundred cubic centimeters per hour. To maintain the mean plasma level of 240 mg. per hundred cubic centimeters approximately 52 mg. of hemoglobin per hundred cubic centimeters per hour would have to be delivered to the plasma. Daily hemolysis for these two days may be estimated according to the foregoing method as equivalent to approximately 200 cc. of the patient's blood (table 2). Similar calculations based on the findings from the sixth to the twentieth day, inclusive, of the attack revealed a total hemolysis equivalent to the hemoglobin content of 880 cc. of the patient's blood.

In summary, it is estimated that the red cells of approximately 2,000 cc. of blood were destroyed intravascularly during the entire hemolytic attack (table 2). During the first fourteen days of the attack, when the red blood cell count and concentration of hemoglobin decreased from 4,710,000 and 94 per cent to 2,920,000 and 59 per cent respectively, the data show destruction of the red cells of 1,850 cc. of the patient's blood. It seems justifiable to conclude from these data that the degree of hemolysis which occurred intravascularly was sufficient to cause the anemia.

Quantitative Estimation of the Extent of Hemolysis Based on Fecal Urobilinogen Excretion.—Unfortunately, the stools representing the first three days of the attack were not available; a stool obtained after an enema on the morning of the fourth day of the attack was discarded and the collection period began from this time. Defecation was regular and daily throughout the period of study; the average weight of the daily stool was 90 Gm.

The hemoglobin and the blood equivalents of the excess of urobilinogen over that to be expected for normal hemoglobin catabolism were calculated according to Watson's method.[30] Watson estimated that normally 0.46 per cent of the hemoglobin of the blood was excreted daily as urobilinogen. The hemoglobin equivalent of the urobilinogen is estimated from the formula: 41.8 mg. of urobilinogen = 1 Gm. of hemoglobin. The total fecal urobilinogen excretion for the nineteen days of the study, from the fourth to the twenty-second day, inclusive, after the onset of the attack (figure) was 6,000 mg. With the average

TABLE 2.—*Total Amount of Hemolysis Occurring During the Attack of Hemoglobinuria, as Estimated from the Values for Plasma Hemoglobin*

Day After Onset of Hemoglobinuria	Amount of Hemolysis, Gm. of Hemoglobin	Hemoglobin in Whole Blood, Gm. per 100 Cc.	Volume of Blood Destroyed, Cc.
1	38.7 *	....	365 *
2	38.7	....	365
3	35.1	14 6	245
4	26.8	14.2	205
5	26.8	12.6	210
6	14.3	11.8	125
7	11.4	11.4	100
8	8.3	11.0	80
9	8.3	....	80
10	5.2	10.0	55
11	5.2	....	55
12	5.2	9.8	55
13	5.2	....	55
14	5.2	9.2	55
15	5.2	....	55
16	5.2	9.3	55
17	3.6	....	40
18	3.6	9.3	40
19	1.5	....	15
20	1.5	....	15
21	0.0	10.3	0
22	0.0	....	0
Total	255.0		2,070

* The concentration of hemoglobin in the plasma on the first day of the attack, before admission to the hospital, was not obtained. As discussed in the text, hemolysis was probably at least as great on this day as on the one following.

hemoglobin value of 10.4 Gm. per hundred cubic centimeters of blood for the entire period and the calculated blood volume of 4,700 cc., the circulating hemoglobin was 490 Gm. According to Watson's value of 0.46 per cent, this total blood hemoglobin would normally result in a daily excretion of 95 mg. of urobilinogen ($490 \times \frac{0.46}{100} \times 41.8 = 95$ mg.), or 1,790 mg. for the nineteen days of study. There was, therefore, 4,210 mg. of urobilinogen in excess of the expected amount under

30. Watson, C. J.: The Pyrrol Pigments, with Particular Reference to Normal and Pathologic Hemoglobin Metabolism: IV. Rate of Hemoglobin Metabolism, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 4, p. 2506.

conditions of normal hemoglobin catabolism. This amount of urobilinogen is equivalent to 101 Gm. of hemoglobin ($\frac{4,210}{41.8}$), or the hemoglobin of approximately 1,000 cc. of the patient's blood, with an average hemoglobin concentration of 10.4 Gm. per hundred cubic centimeters. This figure of 1,000 cc. of blood destroyed during the fourth to the twenty-second day, inclusive, of the attack as calculated by this method is to be compared with the value of 1,300 cc. of blood destroyed as calculated from the plasma hemoglobin values for the same period.

The finding that the amount of blood destroyed as calculated from the urobilinogen excretion was not greater than the amount destroyed as calculated from the values for plasma hemoglobin demonstrated that the blood destruction was entirely "intravascular," i. e., that the hemoglobin from the blood destroyed was liberated into the circulation. This is in contrast to the findings in cases of well recognized types of hemolytic crises, in which severe anemia may develop rapidly without the appearance in the circulation of any, or sometimes only a small amount, of the hemoglobin of the blood destroyed.[31]

Nature of the Hemoglobin Pigments of Plasma and Urine.—As noted previously, spectrophotometric studies on the third day of the attack revealed oxyhemoglobin in both the plasma and the urine, and in addition, a band at 619 millimicrons in the plasma and a similar faint band in the urine. There was no methemoglobin either in the plasma or in the urine. An absorption band at 576 millimicrons and one at approximately 620 millimicrons were observed with a Zeiss hand spectroscope in several samples of plasma during the following ten days. From the sixth to the sixteenth day after the onset of the attack, when the plasma hemoglobin according to the benzidine reaction was 122 to 30 mg. per hundred cubic centimeters, the plasma showed a reddish brown to brownish discoloration rather than the red discoloration which we have observed in man at similar levels of plasma hemoglobin after intravenous injections of solutions of hemoglobin and in attacks of march hemoglobinuria. The urine, on the other hand, showed only oxyhemoglobin with a hand spectroscope and was more reddish than the plasma even when the urinary concentration of hemoglobin, according to the benzidine reaction, was less than that of the plasma.

The brownish discoloration of the plasma and the absorption band at 619 millimicrons demonstrated the presence of methemalbumin, a brown pigment which has been described only recently.[32] Using a

31. Gilligan, D. R., and Kapnick, I.: Clinical and Laboratory Observations on Hemoglobinuria Occurring During Sulfanilamide Therapy, New England J. Med. **224**:801, 1941. Dameshek and Schwartz.[20]

32. Fairley, N. H.: Methaemalbumin in Man (Pseudo-Methaemoglobin), Proc. Roy. Soc. Med. **32**:1278, 1939.

Hartridge reversion spectroscope, Fairley [33] found the point of maximum absorption of the alpha band of this pigment at 623 millimicrons, and Heilmeyer,[34] using a Köning-Martens type of spectrophotometer, which we also employed in our studies, found the point of maximum absorption of the alpha band at 620 millimicrons. Methemalbumin apparently occurs in the plasma when the hemoglobin molecule in the circulation is split into heme and globin and the heme is oxidized to hematin, which promptly unites with the crystalbumin of the plasma.[32] Ham [35] and we too have noted this brownish discoloration of the plasma in patients with Marchiafava-Micheli disease when the concentration of hemoglobin, as measured by the benzidine test, was between 25 and 60 mg. per hundred cubic centimeters. Fairley [33] has identified methemalbumin by spectrophotometric examination of the plasma of patients with blackwater fever, those with paroxysmal nocturnal hemoglobinuria and those experiencing transfusion reactions. An absorption maximum at approximately this same wavelength also has been reported to be present in the serum in some other hemolytic conditions.[36] This pigment was not observed on spectrophotometric analysis of the plasma of patients with march hemoglobinuria recently studied in this laboratory.[1b] We have never noted this brownish discoloration of the plasma in cases of hemoglobinemia following intravenous injection of 1.5 to 16.0 Gm. of hemoglobin [1a] or during either the hemoglobinemia of march hemoglobinuria [1b] or the physiologic hemoglobinemia occasioned in normal subjects by long runs.[37] Apparently, methemalbumin is found only in cases of a higher degree of hemoglobinemia or of more prolonged hemoglobinemia in which some of the hemoglobin remains in the circulation for a considerable period; the presence of this pigment is, therefore, of no diagnostic significance.

Effect of Exercise on Hemoglobinemia and Hemoglobinuria in Our Patient and in a Patient with Marchiafava-Micheli Disease.—By the seventh day after the onset of the attack our patient's hemoglobinuria had subsided markedly, so that the urine was straw colored and showed

33. Fairley, N. H.: The Fate of Extracorpuscular Circulating Hemoglobin, Brit. M. J. **2**:213, 1940.

34. Heilmeyer, L.: Medizinische Spectrophotometrie, Jena, Gustav Fischer, 1934, p. 121.

35. Ham, T. H.: Personal communication to the authors.

36. Schumm, O.: Ueber den Nachweis von Hämatin im menschlichen Blutserum, Ztschr. f. physiol. Chem. **87**:171, 1913. Feigl, J.: Ueber das Auftreten von Hämatin im Blute bei Vergiftung mit Chloraten, Biochem. Ztschr. **74**:394, 1916; Chemische Blutuntersuchungen an der Teilnehmern eines Armes-Gepäckmarsches. I. Ueber Umsatz und Ausscheidung von Blutfarbstoff. Hämoglobinämie, Hämatinämie und Hämoglobinurie, ibid. **76**:88, 1916.

37. Gilligan, D. R.; Altschule, M. D., and Katersky, E. M.: Unpublished data.

only a small concentration of hemoglobin, according to the benzidine test. The plasma hemoglobin level had decreased to 70 mg. per hundred cubic centimeters (figure). The patient was for the first time allowed to be up and about the ward for some hours, whereupon the urine again became pink. The average concentration of the urinary hemoglobin for this day was 20 mg. per hundred cubic centimeters. The patient remained in bed on the following two days. The plasma hemoglobin decreased during this period to 31 mg. per hundred cubic centimeters. On the morning of the tenth day the urine was free of hemoglobin, but after the patient had been up and about the ward for a short period the urine again showed a trace of hemoglobin.

The suggestion afforded by these observations, that the hemolytic process was exacerbated by exertion, was further tested by having the patient walk 0.5 mile (0.8 kilometer) in thirteen minutes. On this exertion, the plasma hemoglobin increased from 31 to 50 mg. per hundred cubic centimeters and the urine became light red and showed concentrations of hemoglobin up to 51 mg. per hundred cubic centimeters (table 3). The hemoglobin in the urine then decreased to an immeasurable trace in the following three hours of rest in bed. Two days later the walk was repeated, with similar results. Several days later, when the plasma hemoglobin was 28 mg. per hundred cubic centimeters, it was demonstrated that standing still in the upright position also evoked a small increase in plasma hemoglobin and slight hemoglobinuria (table 3). On the nineteenth day after the onset of the attack, when the plasma hemoglobin had decreased to 12 mg. per hundred cubic centimeters, standing no longer evoked appreciable hemoglobinemia or hemoglobinuria, and two days later, when the plasma hemoglobin had become normal, a walk of 1.1 miles (1.7 kilometer) in thirty minutes produced neither hemoglobinemia nor hemoglobinuria (table 3). The same exertion ten days later, and again several months later, also failed to produce hemolysis.

In connection with these findings demonstrating increased hemolysis on exercise during the hemolytic attack, the question arises whether a patient with hemoglobinemia from any cause may likewise show increased hemolysis on exercise. Data concerning this question are meager. In patients with Marchifava-Micheli disease and constant hemoglobinemia exacerbation of hemolysis does not occur during the day, but rather there is partial recovery from the hemolytic attacks which occur during sleep.[13] We have had the opportunity to study the effect of exercise on the degree of hemolysis in a patient with Marchiafava-Micheli disease referred to us by Dr. Ham. The data for this patient showed no effect of exercise on the amount of hemoglobin in the plasma or the urine (table 3). It was fortunate that the

TABLE 3.—*Effect of Walking and of Posture on Degree of Hemoglobinemia and Hemoglobinuria in Patient (J. Y.) Reported on Here and in a Patient (L. G.) with Marchiafava-Micheli Disease*

Patient	Date 1940	Day After Onset of Hemoglobinuria	Time	Condition of Patient During Study	Plasma Hemoglobin, Mg./100 Cc.	Urine		
						Hemoglobin		
						Concentration, Mg./100 Cc.	Excreted, Mg./Hr.	"Albumin," * Mg./100 Cc.
J. Y.	4/29	10	5:30 a.m. - 7:00 a.m.	In bed	..	0	0	44
			7:00 a.m. - 12:15 p.m.	In chair	31	Trace	Trace	..
			12:15 p.m. - 1:15 p.m.	Walking 0.5 mile in 13 min.	50	31	9	..
			1:15 p.m. - 2:15 p.m.	In chair	..	51	33	261
			2:15 p.m. - 4:45 p.m.	In chair	..	21	20	..
			4:45 p.m. - 4:30 a.m.	In bed	..	Trace	Trace	14
			4:30 a.m. - 6:00 a.m.	In bed	..	0	0	..
	5/ 1	12	7:20 a.m. - 9:15 a.m.	In bed	..	0	0	6
			9:15 a.m. - 10:45 a.m.	Up and about ward	26	7	7	..
			10:45 a.m. - 11:15 a.m.	Walking 0.5 mile in 11 min.	39	24	16	336
			11:15 a.m. - 12:30 p.m.	In bed	..	16	8	..
			12:30 p.m. - 2:30 p.m.	In bed	..	2	4	..
			2:30 p.m. - 4:30 p.m.	In bed	..	Trace	Trace	..
	5/ 2	13	6:00 a.m. - 10:00 a.m.	In bed and up	..	Trace	Trace	..
			10:00 a.m. - 2:00 p.m.	Up and about ward	40	11	10	239
			2:00 p.m. - 6:00 p.m.	Up and about ward	..	8	6	..
			6:00 p.m. - 10:00 p.m.	Up and to bed	..	1	1	..
			10:00 p.m. - 2:00 a.m.	In bed	..	Trace	Trace	..
			2:00 a.m. - 6:00 a.m.	In bed	..	Slight trace	Trace	114
			10:00 a.m.	In bed	22	..	..	..
	5/ 6	17	10:13 a.m. - 1:25 p.m.	In chair	..	3	3	75
			1:25 p.m. - 2:35 p.m.	In chair	28	3	1	..
			2:35 p.m. - 3:20 p.m.	Standing upright 30 min.	35	12	11	..
			3:20 p.m. - 5:10 p.m.	In chair	..	24	12	172
			5:10 p.m. - 7:00 p.m.	In chair	..	13	11	..
			7:00 p.m. - 5:00 a.m.	In bed	..	Trace	Trace	..
			5:00 a.m. - 7:00 a.m.	In bed	..	0	0	..
	5/ 8	19	10:15 a.m. - 1:25 p.m.	In chair	..	Trace	Trace	..
			1:25 p.m. - 2:05 p.m.	In chair	12	4	6	178
			2:05 p.m. - 3:05 p.m.	Standing in a kyphotic position 30 min.	14	5	5	141
			3:05 p.m. - 3:53 p.m.	Standing upright 30 min.	15	5	6	133
			3:53 p.m. - 7:00 p.m.	In chair	..	Slight trace	Slight trace	..
			7:00 p.m. - 7:00 a.m.	In bed	..	Slight trace	Slight trace	..
	5/10	21	7:00 a.m. - 8:30 a.m.	In bed	8	0	0	48
			8:30 a.m. - 9:45 a.m.	Walking 1.1 mile in 30 min.	8	0	0	50
	5/20	31	7:00 a.m. - 8:30 a.m.	In chair	7	0	0	290
			8:30 a.m. - 9:45 a.m.	Walking 1.1 mile in 30 min.	6	0	0	250
	8/26	129	10:00 a.m. - 10:45 a.m.	Walking 1.1 mile in 30 min.	5	0	0	..
L. G.	6/11	..	8:00 a.m. - 9:15 a.m.	Traveling on train	29	4 †	3	..
			9:15 a.m. - 10:30 a.m.	In bed (awake)	28	0	0	52
			10:30 a.m. - 11:15 a.m.	Walking 1.8 mile in 30 min.	30	0	0	48

concentration of plasma hemoglobin before exercise in this patient was almost identical with that obtained before the exercise which produced hemoglobinuria in our patient.

The exacerbation of hemolysis by exercise occurring during the hemolytic attack in our patient is not characteristic, therefore, of all syndromes with intravascular hemolysis.

Renal Function.—The nonprotein nitrogen level of the blood was elevated to 90 mg. per hundred cubic centimeters on the day after admission. The creatinine content of the blood was 3.2 mg. per hundred cubic centimeters, and the total plasma protein, 6.7 Gm. per hundred cubic centimeters. The corrected sedimentation index was 0.61. The nonprotein nitrogen gradually decreased to 62 mg. per hundred cubic centimeters a week after admission and remained at approximately this level during the following two weeks of the attack. The volume of urine when fluid was forced during the attack was approximately 2,000 cc. per twenty-four hour period, with slightly larger values at night than during the day; the specific gravity of the day and the night specimens and of many individual specimens during twenty-four hour periods varied only between 1.008 and 1.012. The urine contained protein throughout the three weeks of the attack, in amounts related to the degree of hemoglobinuria. During severe hemoglobinuria the "albumin" [38] output (i. e., total protein minus hemoglobin) was 5 to 6 Gm. a day (figure); subsequently, when hemoglobin was absent from the urine or was present only in traces, the daily "albumin" output was 0.3 to 1.3 Gm. (figure). The urinary sediment showed a few red and a few white blood cells and rare brown granular casts. The urine was maintained alkaline throughout the period of massive hemoglobinuria. The amount of urinary sediment was always small; repeated examination failed to reveal any hemoglobin casts or hemosiderin granules. The urea clearance was 20 per cent of normal, with a blood urea nitrogen value of 44 mg. per hundred cubic centimeters, on the third day after admission. On the sixteenth day the clearance was 19 per cent of normal, with a blood urea nitrogen value of 28 mg. per hundred cubic centimeters.

During the two months after the end of the attack the nonprotein nitrogen value decreased to 33 mg. per hundred cubic centimeters and remained between this level and 40 mg. per hundred cubic centimeters during the remainder of the follow-up study. The urea clearance six months after the attack was 99 per cent of normal, with a blood urea nitrogen value of 13.5 mg. per hundred cubic centimeters. There was only a slight trace of albumin in the urine (12 mg. per hundred cubic centimeters) at this time, and the urinary sediment showed, as on all previous occasions, only small numbers of formed elements.

38. No studies were made to identify the nature of this protein fraction.

The temporary reduction of renal function in this patient was interpreted as secondary to the hemolytic attack; the clinical and laboratory findings did not suggest any primary acute renal disease. Fairley and Bromfield [39] consistently observed rises in blood urea and either polyuria or oliguria in patients with the hemoglobinuria of blackwater fever; in the patients who recovered, the blood urea returned to normal a few days to two weeks after cessation of hemoglobinuria. Studies of urea clearance during hemoglobinuria due to intravenous injection of hemoglobin and during march hemoglobinuria showed no reduction in renal function [1]; the hemoglobinuria, however, in these instances was neither of as great a degree nor of as long a duration as in this case. In cases of Marchiafava-Micheli disease, with hemoglobinemia and hemoglobinuria persisting for several years, renal function is markedly reduced; constant hemosiderinuria is observed in such instances. The absence of hemoglobin casts and the sparsity of all types of casts in this patient's urine show that significant tubular obstruction was not present; it is to be remembered that the urine was maintained alkaline to prevent precipitation of hemoglobin products in the tubules.

Hepatic Function.—The liver of this patient was palpable, appeared enlarged on roentgenographic examination during the time of the hemolytic attack and remained enlarged during the period of follow-up study.

Bilirubinemia and moderate jaundice resulted from the hemolytic attack. The amount of intravascular hemolysis was considered great enough to explain the temporary increase in plasma bilirubin without invoking impaired hepatic function as the cause; with an associate,[18] we have previously shown that the plasma bilirubin increased in normal subjects after single intravenous injections of amounts of hemoglobin which induced lower plasma hemoglobin concentrations than the levels present in this patient during the first four days of the hemolytic attack. The question has been raised in the past whether jaundice can occur in hemolytic crises solely because of overproduction of bilirubin or whether icterus results both from increased bilirubin production and from decreased excretory capacity of the liver for bilirubin. In many hemolytic crises, severe anemia and jaundice develop rapidly and simultaneously, so that anoxia is present at the time the level of bilirubin is elevated; the relative importance of the blood destruction itself and of anoxia and its possible effect on hepatic function in the causation of bilirubinemia cannot be evaluated in such instances. In this case jaundice developed in the absence of anemia. As the rate of hemolysis decreased, the plasma bilirubin promptly returned to normal. The

39. Fairley, N. H., and Bromfield, R. J.: Laboratory Studies in Blackwater Fever: III. A New Blood Pigment in Blackwater Fever and Other Biochemical Observations, Tr. Roy. Soc. Trop. Med. & Hyg. **28**:307, 1934.

absence during the height of the jaundice of bile in the urine, the normal urinary urobilinogen, i. e., 1 to 4 mg. per day, and the plasma cholesterol value of 297 mg. per hundred cubic centimeters, with 40 per cent esters, afforded additional evidence that the hepatic function was normal.

SUMMARY

A case of acute, massive hemoglobinemia and hemoglobinuria of obscure cause, in which moderate jaundice and anemia developed, is reported. Hemoglobinemia and hemoglobinuria were greatest during the first days after the onset of the attack and continued for approximately three weeks.

The red blood cell count decreased during the first two weeks of the attack from 4,710,000 to 2,900,000 and the concentration of hemoglobin in the blood decreased from 94 to 59 per cent. Clinical jaundice increased during the first four days of the attack and then gradually disappeared during the following week.

The spleen and the liver were enlarged during the attack; subsequently the size of the spleen decreased slightly. Renal function was reduced during the attack and subsequently returned to normal. Hepatic function was normal.

Oxyhemoglobin and methemalbumin were identified spectrophotometrically in the plasma. The urinary pigment was chiefly oxyhemoglobin.

Quantitative studies of the hemoglobin of the plasma and the urine and quantitative studies of the fecal output of urobilinogen revealed the extent of hemolysis during the attack. Calculations based on the values for hemoglobin in the plasma and in the urine indicated hemolysis of the red cells of approximately 1,400 cc. of the patient's blood during the first week of the attack, of 400 cc. during the second week and of 200 cc. during the third.

Calculations based on excretion of urobilinogen in the stools collected from the fourth to the nineteenth day after the onset of hemoglobinuria indicated hemolysis of approximately 1,000 cc. of blood during this period, as compared with hemolysis of approximately 1,300 cc. for the same period as calculated from the values for plasma hemoglobin.

The slow development of moderate anemia and moderate jaundice accorded with the amount of blood destruction represented by these calculations. The correspondence between the amounts of blood destroyed during the attack as calculated from the values for plasma hemoglobin and from the total urobilinogen excretion demonstrated that all of the hemoglobin from the blood destroyed during the attack was released into the circulation. This situation is contrasted with

that in the hemolytic attacks occurring in some conditions in which more severe anemia develops with greater rapidity and yet in which there may be no evidences of "intravascular" hemolysis.

During the later stages of the hemolytic attack in this patient it was demonstrated that walking caused a definite but slight exacerbation of hemolysis; after the end of the attack, hemolysis could not be induced by walking or by standing. Exacerbation of hemolysis on walking did not occur in a patient with Marchiafava-Micheli disease with associated hemoglobinemia.

The clinical manifestations and the laboratory findings in this case were not typical of those in any recognized type of hemolytic attack. No autoagglutininins could be demonstrated in the blood of this patient when tests were made on serum incubated in the cold or at body or room temperature. The fragility of the red cells to hypotonic solutions of sodium chloride was normal. The differential diagnosis of hemoglobinuria is discussed.

Progress in Internal Medicine

DISEASES OF THE ADRENAL GLANDS

I. ADDISON'S DISEASE

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Since one of us (E. J. K.)[1] reviewed for this journal the literature dealing with the diseases of the adrenal glands remarkable progress has been made. Crystalline compounds of known chemical structure have been isolated from the adrenal cortex, and one of these subsequently has been synthesized. The pharmacologic properties of many of these substances have been delineated in detail. As a result the treatment of Addison's disease has improved greatly. Better methods for the recognition of Addison's disease have been developed. The ramifications of the physiologic abnormalities of adrenal cortical insufficiency have been explored further. Knowledge of the relation of the adrenal cortex to the constellation of physiologic processes which pertain to sex has been materially advanced, and, in addition, many experimental studies which are concerned with "interglandular relations" have been conducted. Finally, the therapeutic potentialities of adrenal cortical substances for the treatment of disorders which are not primarily adrenal in origin have been investigated and the results reported. In each of these broad fields of endeavor many isolated bits of factual material have been gathered which at present cannot readily be inserted into the general mosaic. These we have deliberately ignored, not, however, without considerable misgiving.

An all-embracing review of this material would be of little value to most clinicians. We therefore decided to limit our survey to the literature which appeared to have clinical significance at present or which promised to have a bearing on clinical problems in the not too distant future. However, in dealing with the pathologic physiology of adrenal

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1. Kepler, E. J.: Diseases of the Adrenal Glands: A Review with Special Reference to the Clinical Aspects, Arch. Int. Med. **56**:105-135 (July) 1935.

cortical insufficiency it was necessary often to deviate from this criterion. Consequently, considerable space is devoted to studies in which experimental animals were used. Whether the results that were obtained from such studies are directly applicable to clinical medicine remains to be seen. In many instances we can be reasonably safe in assuming that they are not. Considerable attention also was given to certain work involving fundamental principles of electrolyte and water metabolism. Whether these studies should have been reviewed at this particular time for this particular journal was a moot question. This material was included because clinicians generally have not appreciated its significance and also because it bears directly on other pathophysiologic processes comparable to those which are encountered in adrenal cortical insufficiency. After all, the continued interest of clinicians in diseases of the adrenal glands arises largely from the fact that in a sense they are key disorders, the understanding of which would illuminate many of the perplexing problems which arise in everyday medical practice.

Our review, then, is distinctly selective rather than comprehensive. In the preparation of any review of this type the personal interests, tastes and prejudices of the authors usually insert themselves. This cannot be avoided; nevertheless, we apologize for it.

PATHOLOGY OF ADDISON'S DISEASE

In 1934 Snell [2] called attention to the fact that the incidence of adrenal cortical atrophy (in comparison with tuberculosis) as a cause of fatal Addison's disease appeared to be increasing. More recently Cragg [3] and Wells and his associates [4] have observed that this trend persists. The latter authors suggested that the widespread use of drugs which have been introduced in recent years may be responsible for the apparent increase of adrenal cortical atrophy. They cited 2 instances in which adrenal cortical atrophy occurred in patients who were treated for pemphigus by the administration of germanin. Talbott and associates [5] criticized the inferences drawn by Wells and his co-workers and

2. Snell, A. M.: The Treatment of Addison's Disease, Proc. Staff Meet., Mayo Clin. **9**:57 (Jan. 24) 1934.

3. Cragg, R. W.: Personal communication to the authors.

4. Wells, H. G.: Addison's Disease with Selective Destruction of the Suprarenal Cortex, Arch. Path. **10**:499-523 (Oct.) 1930. Wells, H. G.; Humphreys, E. M., and Work, E. G.: Significance of the Increased Frequency of Selective Cortical Necrosis of the Adrenal as a Cause of Addison's Disease, J. A. M. A. **109**:490-493 (Aug. 14) 1937.

5. Talbott, J. H.; Lever, W. F., and Consolazio, W. V.: Metabolic Studies on Patients with Pemphigus in Relation to Effects of Cortical Extract and Sodium Chloride, J. Invest. Dermat. **3**:31-68 (Feb.) 1940.

called attention to 2 cases of pemphigus in which associated adrenal cortical hemorrhages were observed at necropsy. They implied that the lesions described by Wells may have been the result of the pemphigus per se.

The apparently increased incidence of adrenal cortical atrophy at necropsy does not necessarily imply that this condition is actually on the increase. If the incidence of tuberculosis of the adrenal cortex is decreasing or if the length of life of patients having this condition is being extended, the incidence of adrenal cortical atrophy at necropsy would be relatively increased. Irrespective of its interpretation, the fact remains that Snell, Cragg and Wells all have found that cortical atrophy now accounts for about half of the cases of fatal Addison's disease, whereas formerly tuberculosis was the etiologic factor in about 90 per cent of cases.

PATHOLOGIC PHYSIOLOGY

Interest in the pathologic physiology of adrenal cortical insufficiency continues to center chiefly on electrolyte metabolism, renal dysfunction and carbohydrate metabolism.

Electrolyte Metabolism.—Sodium: Loeb,[6] in 1932, observed an unusually low concentration of sodium and chloride in the serum of 3 patients who had Addison's disease. One of these patients was benefited by the administration of large amounts of sodium chloride and remained in a state of reasonably good health for five months. At this time the appearance of peripheral edema led to the discontinuance of treatment with sodium chloride, and a crisis of adrenal cortical insufficiency was precipitated.[7] The latter report stimulated a tremendous interest in the relation of the adrenal cortex to the metabolism of electrolytes.

From experimental observations on dogs and rats, it was evident [8] that after adrenalectomy the excretion of sodium and chloride in the urine was increased. This was prevented by administration of a crude extract of the adrenal cortex.[8b] Since the loss of sodium appeared to be

6. Loeb, R. F.: Chemical Changes in the Blood in Addison's Disease, Science **76**:420-421 (Nov. 4) 1932.

7. Loeb, R. F.: Effect of Sodium Chloride in Treatment of a Patient with Addison's Disease, Proc. Soc. Exper. Biol. & Med. **30**:808-812 (March) 1933.

8. (*a*) Loeb, R. F.; Atchley, D. W.; Benedict, E. M., and Leland, J.: Electrolyte Balance Studies in Adrenalectomized Dogs with Particular Reference to the Excretion of Sodium, J. Exper. Med. **57**:775-792 (May) 1933. (*b*) Harrop, G. A.; Soffer, L. J.; Ellsworth, R., and Trescher, J. H.: Studies on the Suprarenal Cortex: III. Plasma Electrolytes and Electrolyte Excretion During Suprarenal Insufficiency in the Dog, ibid. **58**:17-38 (July) 1933. (*c*) Rubin, M. I., and Krick, E. T.: The Salt and Water Metabolism of Adrenal Insufficiency and Partial Starvation in Rats, J. Clin. Investigation **15**:685-695 (Nov.) 1936.

of greater magnitude than that of chloride,[9] it was suggested that the adrenal cortex primarily influenced the metabolism of sodium.[10]

Efforts to compensate for this unusual excretion of sodium and chloride by administration of sodium chloride, either alone or in conjunction with sodium bicarbonate, resulted in prolongation of the lives of adrenalectomized animals. This treatment, however, was not accompanied by return of a completely normal pattern of electrolytes in the plasma, and the animals eventually died. Swingle[11] concluded from this that sodium chloride alone was not a complete substitute for extracts of the adrenal cortex in the treatment of adrenalectomized animals.

Potassium: The metabolism of potassium also appears to be disturbed in cases of adrenal cortical insufficiency. That the concentration of this ion increases in the plasma of animals dying in crisis has been known for some time.[12] This increase in concentration apparently is related to decreased excretion of potassium by the kidney.[13] Conversely, recovery from adrenal cortical insufficiency is associated with the excretion of unusually large amounts of potassium in the urine. Analysis of tissue[14] removed from adrenalectomized animals suggested that the increase in the concentration of potassium in the serum is associated with a simultaneous increase in the content of potassium both in the interstitial fluid and in the cells themselves.[14] This has been interpreted as a passive response to the retention of potassium, which the kidney appears unable to excrete.

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9. Such a loss might have been anticipated in view of the fact that blood plasma and interstitial fluids contain more sodium than chloride.

10. (*a*) Harrop, G. A.; Soffer, L. J.; Nicholson, W. M., and Strauss, M.: Studies on the Suprarenal Cortex: IV. The Effect of Sodium Salts in Sustaining the Suprarenalectomized Dog, J. Exper. Med. **61**:839-860 (June) 1935. (*b*) Allers, W. D.: The Influence of Diet and Mineral Metabolism on Dogs After Suprarenalectomy, Proc. Staff Meet., Mayo Clin. **10**:406-409 (June 26) 1935. (*c*) Loeb and others.[6a]

11. Swingle, W. W.; Pfiiffner, J. J.; Vars, H. M., and Parkins, W. M.: The Effect of Sodium Chloride Administration upon Adrenalectomized Dogs Not Receiving Extract, Am. J. Physiol. **108**:159-167 (April) 1934.

12. Hastings, A. B., and Compere, E. L.: Effect of Bilateral Suprarenalectomy on Certain Constituents of the Blood of Dogs, Proc. Soc. Exper. Biol. & Med. **28**:376-378 (Jan.) 1931.

13. Harrop, G. A.; Nicholson, W. M., and Strauss, M.: Studies on the Suprarenal Cortex: V. The Influence of the Cortical Hormone upon the Excretion of Water and Electrolytes in the Suprarenalectomized Dog, J. Exper. Med. **64**:233-251 (Aug.) 1936.

14. Harrison, H. E., and Darrow, D. C.: The Distribution of Body Water and Electrolytes in Adrenal Insufficiency, J. Clin. Investigation **17**:77-86 (Jan.) 1938.

The significance of the dietary intake of potassium was emphasized first by Allers, Nilson and Kendall.[15] They and others[16] found that adrenalectomized dogs treated with sodium salts could be maintained indefinitely with normal concentrations of electrolytes in the plasma if the intake of potassium was restricted. This situation was in contrast to the difficulties often encountered when the content of potassium in the diet was disregarded.[17] The clinical significance of these observations has been emphasized by Wilder and his associates,[18] and the potassium content of foods and the technic of preparing diets of known content of potassium have been reported by Sister Mary Victor.[19] Patients who had Addison's disease received a diet low in potassium (1.6 Gm.) and high in sodium (7.3 Gm.). They reacted unfavorably to an increase in the daily intake of potassium to the amount present in the usual unselected diet (4 Gm.). This sensitivity to potassium in the diet appeared to be more noticeable among patients who were depleted of sodium[20] and was less marked when sodium saturation had been accomplished by previous administration of sodium chloride. The mechanism by which potassium produces this effect is still unknown. It cannot be accounted for merely by diuresis or by the excessive excretion of sodium that sometimes follows administration of potassium salts to an edematous patient.

Efforts have been made to attribute the muscular weakness which characterizes adrenal cortical insufficiency to the increased concentration of potassium in the serum.[21] The explanation does not seem tenable,

15. Allers, W. D.; Nilson, H. W., and Kendall, E. C.: Studies on Adrenalectomized Dogs: The Toxic Action of Potassium, Proc. Staff Meet., Mayo Clin. **11**:283-288 (April 29) 1936. Allers, W. D., and Kendall, E. C.: Maintenance of Adrenalectomized Dogs Without Cortin, Through Control of the Mineral Constituents of the Diet, Am. J. Physiol. **118**:87-94 (Jan.) 1937. Nilson, H. W.: Corticoadrenal Insufficiency: Metabolism Studies on Potassium, Sodium, and Chloride, ibid. **118**:620-631 (March) 1937.

16. (*a*) Zwemer, R. L., and Truszkowski, R.: The Importance of Corticoadrenal Regulation of Potassium Metabolism, Endocrinology **21**:40-49 (Jan.) 1937. (*b*) Cleghorn, R. A., and McVicar, G. A.: High Potassium Diet and the Survival of Adrenalectomized Rats, Nature, London **138**:124 (July 18) 1936. (*c*) Harrison and Darrow.[14]

17. Harrop and others.[10a] Swingle and others.[11]

18. Wilder, R. M.; Kendall, E. C.; Snell, A. M.; Kepler, E. J.; Rynearson, E. H., and Adams, M.: Intake of Potassium, Important Consideration in Addison's Disease, Arch. Int. Med. **59**:367-393 (March) 1937.

19. Victor, Sister Mary: A Diet Restricted in Potassium, J. Am. Dietet. A. **14**:759-772 (Dec.) 1938.

20. Greene, J. A., and Johnston, G. W.: Electrolyte Balance During Treatment, Crises, and Severe Infection in Cases of Addison's Disease, Arch. Int. Med. **66**:1052-1059 (Nov.) 1940.

21. Footnote 16 *a* and *b*.

however, since in other conditions, such as some types of nephritis,[22] elevation in the concentration of potassium is not necessarily associated with profound weakness. Recently, Miller and Darrow observed that artificially produced increases or decreases in the concentration of potassium in the serum of normal rats have no effect on either voluntary [23] or involuntary [24] contraction of muscle.

In a recent review, Fenn [25] emphasized present day ignorance of the physiology of potassium. It appears that this ion is intimately related to many physiologic processes which are incompletely understood.

Renal Function.—The abnormal function of the kidney in cases both of experimental adrenal insufficiency and of Addison's disease has received some study. This subject is of fundamental importance because it bears directly on one of the unsolved problems of adrenal cortical function, namely, the site of action of adrenal cortical substances. The question arises whether such substances exert their influence primarily and specifically on the cells of the kidney or whether they affect the behavior of most, if not all, the cells in the organism. If the latter is true, the distinctive type of renal insufficiency which accompanies Addison's disease would represent only the renal aspects of profound changes taking place within the cells of the body as a whole.

Harrison and Darrow [26] attacked this problem by measuring the ability of the kidneys of adrenalectomized animals to remove sodium and potassium from the blood stream. They demonstrated that clearance of sodium was increased and clearance of potassium decreased in adrenalectomized animals after treatment with adrenal cortical extract was discontinued. Resumption of specific treatment restored the values for these clearances to normal. They concluded that marked disturbance in renal function of a specific type occurred after adrenalectomy and stated: " . . . the primary change is a failure of the renal tubules to maintain the necessary concentration differences between urine and plasma with respect to certain ions."

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22. The observations of Rabinowitch, Nelken and Steinitz and Bolliger and Breh were cited by Harrison and Darrow.[14]

23. Miller, H. C., and Darrow, D. C.: Relation of Serum and Muscle Electrolyte, Particularly Potassium, to Voluntary Exercise, Am. J. Physiol. **132**:801-809 (April) 1941.

24. Miller, H. C., and Darrow, D. C.: The Effect of Changes in Muscle Electrolyte on the Response of Skeletal Muscle to Tetanic Stimulation with Particular Reference to Potassium, Am. J. Physiol. **129**:264-270 (May) 1940.

25. Fenn, W. O.: The Role of Potassium in Physiologic Processes, Physiol. Rev. **20**:377-415 (July) 1940.

26. Harrison, H. E., and Darrow, D. C.: Renal Function in Experimental Adrenal Insufficiency, Am. J. Physiol. **125**:631-643 (April) 1939.

There is some evidence, according to Willson and Sunderman,[27] to indicate that although the kidneys of patients who have Addison's disease ordinarily secrete too much sodium chloride, under certain conditions they cannot secrete enough. For example, a large amount of sodium chloride (15 Gm. in addition to that contained in the diet) and small amounts of water (600 cc. daily) were administered to patients who had Addison's disease; the maximal concentrations of sodium and chloride in the urine were significantly less than those in the urine of normal persons treated in this manner. Because of this limited power to concentrate sodium in the urine, a definite positive balance for sodium and chloride developed in 2 patients who had Addison's disease, whereas it did not develop in persons without the disease. Furthermore, during this period when the maximal concentrations of sodium and chloride were being maintained, the kidneys secreted a relatively large volume of urine in comparison with the amount of water ingested. Such a negative water balance in cases of Addison's disease maintained for any length of time results in the clinical picture of crisis in spite of the fact that the body is, figuratively speaking, pretty well saturated with sodium chloride. This observation lends support to the idea that renal function is severely deranged in the presence of Addison's disease.

The largely functional character of this renal disorder, however, is suggested by the fact that it is not permanent and can be corrected for the most part by administration of adrenal cortical compounds.[26] The absence of significant histologic changes in the kidneys in cases of fatal adrenal insufficiency further supports the view.[28]

In addition, acute adrenal insufficiency is associated with secondary disturbances in renal function[29] which are similar to those observed in cases of dehydration or shock from any cause and which are sometimes referred to under the term extrarenal azotemia. In the case of acute adrenal insufficiency these disturbances appear to result largely from diminished glomerular filtration and manifest themselves in part by diminished clearance and by retention of urea and potassium.

Changes in the Body Fluids in Addison's Disease.—The crisis of Addison's disease is characterized by a shocklike state which is asso-

27. Willson, D. M., and Sunderman, F. W.: Studies in Serum Electrolytes: XII. The Effect of Water Restriction in a Patient with Addison's Disease Receiving Sodium Chloride, J. Clin. Investigation **18**:35-43 (Jan.) 1939. Willson, D. M.: Electrolyte Balance Studies in Addison's Disease, Thesis, University of Minnesota Graduate School of Medicine, 1940.

28. Gersh, I., and Grollman, A.: Kidney Function in Adrenal Cortical Insufficiency, Am. J. Physiol. **125**:66-74 (Jan.) 1939.

29. Smith, H. W.: Kidney, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Stanford University Press, 1939, vol. 1, pp. 505-529.

ciated with a decrease in the volume of circulating blood.[30] There is considerable evidence that the volume of interstitial fluid[31] is likewise reduced. Several factors appear to operate in the production of these changes.

One of these factors is the urinary loss of fluid which occurs at the onset of a crisis of adrenal insufficiency.[30] This loss, coupled with the usually associated condition of anorexia and diminished ingestion of fluid, results in a negative balance of water. Although frequently encountered, this negative water balance does not appear to be essential in the production of shock in Addison's disease. Harrop and associates,[18] for example, demonstrated that in experimental animals hemoconcentration and shock will still occur even though a negative water balance is prevented by forced ingestion of water. This occurrence of shock without actual loss of fluid from the animal suggests that in the crisis of Addison's disease a redistribution of water from one compartment of the body to another may occur. Such a redistribution might readily reduce the blood volume and thereby become fully as important as the loss of a large amount of water from the body by diuresis. This conception is sufficiently important to justify its discussion in some detail.

A visual representation of the body fluids and the channels by which their volume can be changed has been prepared by Gamble[32] (fig. 1). As may be seen, Gamble visualized the fluids of the body in two main compartments. The fluid in the first, or extracellular, compartment comprises about 20 per cent of the weight of the body and consists of the plasma and the interstitial fluid, which is essentially a protein-free dialysate of the plasma. This fluid represents the *milieu intérieur* of Claude Bernard and functions primarily in the transportation of materials to and from the cells. The fluid in the second major compartment consists of that within the cells. The volume of this compartment is larger, and its contents make up approximately 50 per cent of the body weight.

It is generally realized that the volume of plasma remains relatively constant, even though the intake of fluid varies considerably. This constancy is maintained at the expense of the interstitial fluid, which acts

30. Harrop, G. A.; Weinstein, A.; Soffer, L. J., and Trescher, J. H.: Studies on the Suprarenal Cortex: II. Metabolism, Circulation, and Blood Concentration During Suprarenal Insufficiency in the Dog, J. Exper. Med. **58**:1-16 (July) 1933. Swingle, W. W.; Vars, H. M., and Parkins, W. M.: A Study of the Blood Volume of Adrenalectomized Dogs, Am. J. Physiol. **109**:488-501 (Sept.) 1934.

31. Harrop, G. A.: The Influence of the Adrenal Cortex upon the Distribution of Body Water, Bull. Johns Hopkins Hosp. **59**:11-24 (July) 1936.

32. Gamble, J. L.: Extracellular Fluid and Its Vicissitudes, Bull. Johns Hopkins Hosp. **61**:151-173 (Sept.) 1937.

as a large reservoir adding fluid to or removing it from the blood stream as circumstances require. Secondary changes in blood volume occur only when this reservoir is seriously overfilled or depleted.

The migration of water back and forth from the cell to the extracellular space appears to be determined mainly by differences in osmotic pressure on the two sides of the cell membrane. Although the chemical composition of the fluid within the cell is different from that of the extracellular fluid (fig. 2), the osmotic pressures on the two sides of the cell

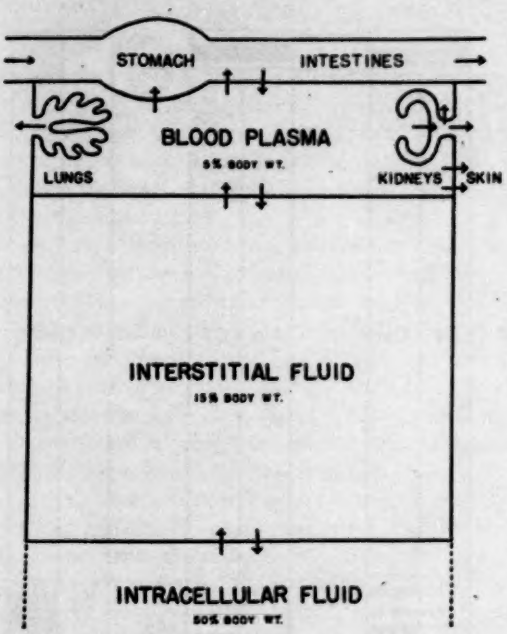

Fig. 1.—The approximate distribution of fluids in the various compartments of the body (Gamble [32]).

membrane remain essentially equal. For practical purposes the osmotic pressure of the interstitial fluid is determined largely by its concentration of sodium.[33]

33. Since more than 90 per cent of extracellular base is sodium, changes in the remaining basic ions have little effect on the concentration of total bases. The acid ions, chloride, bicarbonate and protein, play only a secondary role in the body economy; their total ionic concentration is automatically regulated by respiration and by the kidneys to equal the total concentration of base. For a detailed discussion of this phase of the problem, the reader is referred to the admirable exposition by Gamble.[32]

These basic concepts may be applied to the pathologic physiology of Addison's disease. As adrenal cortical insufficiency increases the following sequence of events may occur: Initially there is a loss of sodium from the body by way of the urine. This loss progresses, and the interstitial fluid becomes more or less depleted of sodium. The osmotic pressure of the interstitial fluid, therefore, decreases relative to that of the cell. To maintain osmotic equilibrium, interstitial water

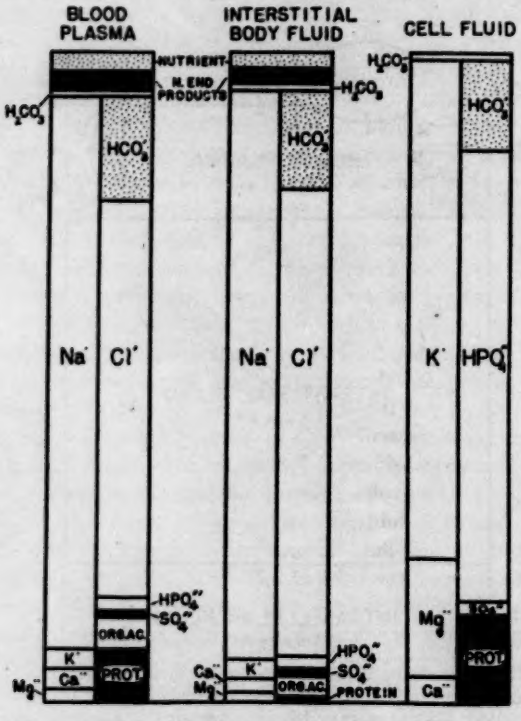

Fig. 2.—The approximate distribution of electrolytes in the various body fluids (Gamble [32]).

migrates into the cell. (The cell membrane [thought to be semipermeable] prevents equalization of osmotic pressure by a movement of electrolytes from the cell into the interstitial fluid.) As a result of this movement of water into the cell the cellular fluid is diluted and the interstitial fluid is concentrated. Osmotic pressures on the two sides of the cell membrane are thereby equalized at the expense of a decreased volume of interstitial fluid. Loss of salt and water continues to occur

by way of the urine, the volume of interstitial fluid continues to decrease and finally the volume of blood itself is diminished.

Although this concept of adrenal cortical insufficiency admittedly is hypothetic, it does have the backing of some experimental evidence. Harrison and Darrow,[14] for example, analyzed muscles obtained from adrenalectomized and from normal animals all of which had been depleted of sodium. They demonstrated that as the concentration of sodium in the extracellular fluid decreased the water content of the cells increased, indicating that water had migrated into the cells. Similar results have been obtained by other workers.[34]

In the evaluation of this concept of adrenal cortical insufficiency and the experimental evidence on which it is based, the limitations of methods for analyzing and measuring the volume of intracellular and extracellular fluids must be remembered. The technics employed are difficult, and the methods yield results which are essentially inferential. In spite of these limitations, the deductions which have been made are worth serious consideration.

The diagram taken from an article by Darrow and Yannet [35] will aid those who have not been particularly interested in this problem (fig. 3). This diagram represents an animal weighing 10 Kg. Under normal conditions, the fluid in the extracellular compartments will amount to 2 liters and the fluid within the cells to 5 liters. Darrow and Yannet stated that the concentration of electrolytes, and hence the osmotic pressure, is normally a little higher within the cells than it is in the fluid in the surrounding interstitial space. On the removal of 100 milliequivalents of electrolytes (such as 5.85 Gm. of sodium chloride) from the extracellular fluid there will be a decrease in the osmotic pressure of the extracellular fluid. To compensate for this, fluid will migrate into the cells, diluting the intracellular fluid and reestablishing osmotic equilibrium. In the instance cited this will lead to a 25 per cent reduction in the volume of extracellular fluid and a corresponding increase in the fluid within the cells. Such a change can result in shock. This type of dehydration is essentially little different in its effect on the volume of blood from the dehydration associated with the direct loss of fluid from

34. Hegnauer, A. H., and Robinson, E. J.: The Water and Electrolyte Distribution Among Plasma, Red Blood Cells, and Muscle After Adrenalectomy, J. Biol. Chem. **116**:769-778 (Dec.) 1936. Muntwyler, E.; Mautz, F. R.; Mangun, G., and Mellors, R. C.: Electrolyte and Water Exchanges Between Muscle and Blood in Adrenal Insufficiency, ibid. **128**:lxxiv (June) 1939. Yannet, H., and Darrow, D. C.: The Effect of Depletion of Extracellular Electrolytes on the Chemical Composition of Skeletal Muscle, Liver, and Cardiac Muscle, ibid. **134**: 721-737 (July) 1940.

35. Darrow, D. C., and Yannet, H.: The Changes in the Distribution of Body Water Accompanying Increase and Decrease in Extracellular Electrolyte, J. Clin. Investigation **14**:266-275 (March) 1935.

the body, as by hemorrhage. In this instance, however, the fluid has not actually been lost; it has migrated into the cells, where it is immobilized.

The converse of this phenomenon is readily apparent. The addition of electrolytes to the extracellular compartment (clinically observed in the retention of sodium which occurs with the administration of desoxycorticosterone) will result in an increase in the osmotic pressure of the extracellular fluid and the migration of fluid from the cells into the interstitial spaces. If these changes are carried to an extreme, hydremia, or increase in the volume of circulating blood, will occur.

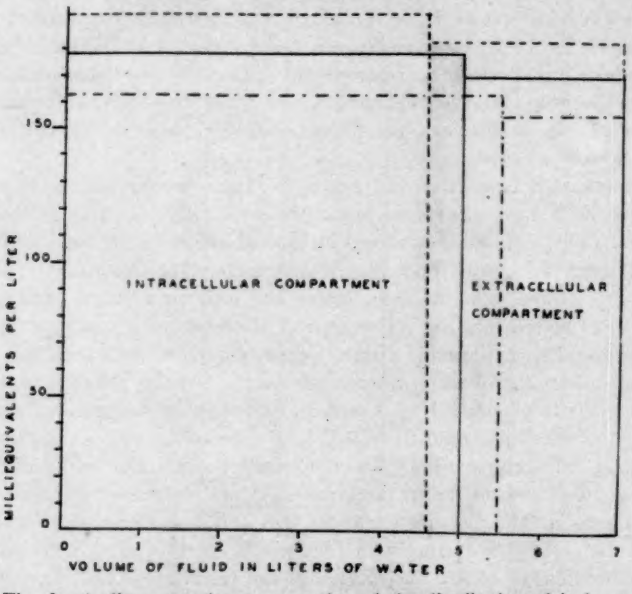

Fig. 3.—A diagrammatic representation of the distribution of body water and electrolytes. The areas bounded by the lines representing volume and concentration indicate the total amount of intracellular or extracellular electrolyte. The solid lines give the distribution under normal conditions; the lines made up of dots and dashes indicate the distribution after the removal of 100 milliequivalents of extracellular electrolyte; the lines made up of dashes represent the distribution after the addition of 100 milliequivalents of extracellular electrolyte (Darrow and Yannet [35]).

Extrarenal Physiology.—The preceding observations concerning the metabolism of water and electrolytes in adrenal insufficiency have dealt primarily with the results of a disordered function of the kidney. It would be incorrect to assume from this, however, that the kidney is the

sole site of the disorder. Observations made on adrenalectomized rats [36] from which the kidneys were removed refute such a hypothesis. It has been demonstrated that such animals do not survive as long as animals which have been merely nephrectomized. Furthermore, the administration of an extract of the adrenal cortex will prolong the survival time and minimize the increase in the concentration of potassium in the plasma of animals from which both the kidneys and the adrenal glands have been removed.

Similarly, Swingle and his associates [37] observed that when adrenal cortical extract was withheld from an adrenalectomized dog the classic symptoms and signs of crisis developed despite the fact that the animal had anuria and thus could not have lost sodium in the urine. These workers [38] also observed that dogs can recover from crisis after administration of large amounts of cortical extract in a period when sodium chloride is not administered and there is no change in the concentration of sodium in the serum.

These and numerous other observations suggest that the adrenal cortex exerts an influence on the organism which is entirely independent of its effect on the kidney. The nature of this influence is incompletely understood at present, however, and the elucidation of this problem is complicated by the technical difficulties which beset investigators of cellular physiology.

Carbohydrate Metabolism.—Evidence which has accumulated for some years indicates that carbohydrate metabolism is influenced by the adrenal cortex. Britton and Silvette [39] were early proponents of this idea. They demonstrated that when the adrenal glands were removed

36. Ingle, D. J., and Kendall, E. C.: Survival of the Adrenalectomized Nephrectomized Rat, Am. J. Physiol. **117**:200-202 (Oct.) 1936. Ingle, D. J.; Nilson, H. W., and Kendall, E. C.: The Effect of Cortin on the Concentration of Some Constituents of the Blood of Adrenalectomized Rats, ibid. **118**:302-308 (Feb.) 1937. MacKay, E. M.; Bergman, H. C., and MacKay, L. L. L.: Serum Potassium and Sodium as Altered by Adrenalectomy and Nephrectomy, ibid. **120**:83-86 (Sept.) 1937. Hartman, F. A., and Dubach, R.: The Effect of Adrenal Preparations on the Adrenalectomized-Nephrectomized Rat, Endocrinology **27**:638-641 (Oct.) 1940.

37. Swingle, W. W.; Parkins, W. M.; Taylor, A. R., and Hays, H. W.: The Influence of Adrenal Cortical Hormone upon Electrolyte and Fluid Distribution in Adrenalectomized Dogs Maintained on a Sodium and Chloride Free Diet, Am. J. Physiol. **119**:684-691 (Aug.) 1937.

38. Swingle, W. W.; Parkins, W. M.; Taylor, A. R., and Hays, H. W.: Relation of Serum Sodium and Chloride Levels to Alterations of Body Water in the Intact and Adrenalectomized Dog, and the Influence of Adrenal Cortical Hormone upon Fluid Distribution, Am. J. Physiol. **116**:438-445 (July) 1936.

39. Britton, S. W., and Silvette, H.: The Apparent Prepotent Function of the Adrenal Glands, Am. J. Physiol. **100**:701-713 (May) 1932.

from the guinea pig, cat and other species hypoglycemic convulsive seizures occurred. In addition, it was found that supplies of glycogen in the liver and muscles of such animals were reduced and that the ability to form hepatic glycogen from injections of dextrose or sodium lactate was diminished.

For a long time the importance of these disturbances of carbohydrate metabolism which occurred after adrenalectomy were overshadowed by the seemingly more important alterations in electrolyte metabolism. Furthermore, the results of the studies of this subject frequently were conflicting or inconclusive. In fact, some writers expressed the opinion that the changes in carbohydrate metabolism which had been encountered were entirely nonspecific phenomena secondary to the malnutrition usually present.

Long, Katzin and Fry [40] reviewed this earlier work and disclosed the reasons for some of the discrepancies in results which had been encountered. For example, they pointed out that different species of animals behave differently after adrenalectomy in respect to the duration of survival and the rapidity with which changes in electrolyte and/or carbohydrate metabolism ensue. In some species fatal alterations in electrolyte metabolism occur so rapidly that changes in carbohydrate metabolism do not become apparent; in others the animal survives long enough to permit marked alterations in the level of blood sugar and the content of hepatic and muscle glycogen to take place. These authors also called attention to the necessity of controlling the intake of food prior to analyzing tissues for glycogen. Some animals refuse food after adrenalectomy; others eat until just before death. Under such circumstances, it is not surprising that discrepant results have been obtained by different workers.

In spite of the difficulties which arise in conducting decisive experiments, it now has been shown, at least in certain species, that carbohydrate metabolism unquestionably is deranged by removal of the adrenal cortex. A summary of some of the various observations follows.

Fasting: Adrenalectomized rats [40] or mice can be maintained in good health for a long time by judicious administration of sodium salts. As long as the animals are fed, normal levels of glycogen in the liver and muscle and of sugar in the blood are maintained. However, fasting adrenalectomized animals lose hepatic glycogen rapidly, ultimately lose glycogen from the muscles and finally, at the end of forty-eight hours, become hypoglycemic and often have convulsions. These changes can be prevented by the administration of adrenal cortical extract. Further-

40. Long, C. N. H.; Katzin, B., and Fry, E. G.: The Adrenal Cortex and Carbohydrate Metabolism, Endocrinology **26**:309-344 (Feb.) 1940.

more, administration of this substance to adrenalectomized rats receiving a normal diet results in a striking increase in the deposition of glycogen in the liver.[41]

Comparable observations were made by Thorn and associates [42] in a case of Addison's disease. The appearance of hypoglycemia in this instance seemed to be related to lack of carbohydrate. Thus, although the patient received a daily diet of average caloric content but composed of large amounts of fat and deficient in carbohydrate, hypoglycemia, in which the value for blood sugar was 55 mg. per hundred cubic centimeters, developed within sixty hours. The symptoms were sufficiently severe to necessitate the intravenous administration of dextrose.

Phlorhizin Diabetes and Gluconeogenesis: As is well known, administration of phlorhizin lowers the renal threshold for dextrose, so that sugar is constantly excreted in the urine as long as the endogenous and exogenous supplies hold out. Since the supply of glycogen available for the formation of dextrose in the fasting animal is limited, it must be concluded that the continued excretion of dextrose is maintained at the expense of protein, the chief endogenous source. Fasting adrenalectomized rats and dogs maintained in health by the administration of sodium chloride alone excrete considerably less sugar after administration of phlorhizin than do normal control animals.[43] This defect can be corrected by the administration of certain crystalline compounds obtained from the adrenal cortex (fully by corticosterone and compound E [17-hydroxy-11-dehydrocorticosterone] but only partially by desoxycorticosterone).[44] This work indicates that in adrenalectomized animals the endogenous supply of dextrose, namely protein, either is deficient in amount or is relatively immobile.

Further studies [45] suggested that the latter of these two possibilities is the more likely and that adrenalectomy in a sense immobilizes protein, so that the rate at which it is converted into dextrose is retarded. Stated somewhat differently, the rate of protein catabolism is diminished.

41. Sprague, R. G.: The Influence of Extract of the Adrenal Cortex on Glycogenesis in Fasting Rats, Proc. Staff Meet., Mayo Clin. **15**:291-294 (May 8) 1940.

42. Thorn, G. W.; Koepf, G. F.; Lewis, R. A., and Olsen, E. F.: Carbohydrate Metabolism in Addison's Disease, J. Clin. Investigation **19**:813-832 (Nov.) 1940.

43. (*a*) Evans, G.: The Adrenal Cortex and Endogenous Carbohydrate Formation, Am. J. Physiol. **114**:297-308 (Jan.) 1936. (*b*) Lewis, R. A.; Kuhlman, D.; Delbue, C.; Koepf, G. F., and Thorn, G. W.: The Effect of the Adrenal Cortex on Carbohydrate Metabolism, Endocrinology **27**:971-982 (Dec.) 1940.

44. Wells, B. B.: The Influence of Crystalline Compounds Separated from the Adrenal Cortex on Gluconeogenesis, Proc. Staff Meet., Mayo Clin. **15**:294-297 (May 8) 1940.

45. Long, Katzin and Fry.[40] Lewis and others.[43b] Wells.[44]

If this were true, it would be expected that adrenalectomy would reduce the amount of nitrogen excreted in the urine. It also would be expected that the dextrose-nitrogen ratio in cases of phlorhizin diabetes would be little affected by adrenalectomy, since both the dextrose and the nitrogen excreted in the urine would be diminished proportionately. Actually, most of these theoretic expectations were observed to be fulfilled in fasting adrenalectomized rats. Divergent results regarding the dextrose-nitrogen ratio have been obtained, however, by some workers.

Although adrenalectomy appears to interfere with the formation of dextrose (and glycogen) from endogenous protein, it appears to have no effect on the metabolism of exogenous protein. Wells and Kendall,[46] for example, have stated:

> Adrenalectomized phlorhizinized rats, when given casein alone, were able to metabolize this protein, excrete the expected amounts of glucose and nitrogen and in every way respond as normal phlorhizinized rats without treatment with any hormone from the adrenal gland. It seems evident that the metabolism of exogenous protein is not seriously disturbed by the absence of the adrenal cortical hormones.

Experimental Diabetes: That adrenalectomy reduces the amount of sugar which appears in the urine of totally depancreatized animals has been known for some time. Long, Katzin and Fry [40] investigated this phenomenon further and found that it also occurred if the animal (rat) was only partially depancreatized. They also demonstrated that administration of adrenal cortical extract caused a return of sugar in the urine to the level that was present before the adrenal glands were removed. In fact, if sufficient amounts of adrenal cortical extract were administered, the degree of glycosuria which ensued actually was greater than that which was present before adrenalectomy. Furthermore, these authors noted that adrenal cortical extract intensified the excretion of sugar in partially depancreatized rats that had intact adrenal cortices.

Sprague,[41] in confirming these observations, demonstrated that the administration of adrenal cortical extract to partially depancreatized rats was followed by an increased amount of glycogen in the liver, even though the animals were fasting. From these observations it would appear that although adrenal cortical extracts have the capacity of intensifying one aspect (namely, glycosuria) of experimental diabetes in rats, they also tend, by causing increased storage of glycogen, to ameliorate another.

Insulin: Considerable difference has been observed in the responses of normal and of adrenalectomized animals to intravenous injection of small amounts of insulin. Lewis [43b] and his associates disclosed that

46. Wells, B. B., and Kendall, E. C.: The Influence of the Adrenal Cortex on Phlorhizin Diabetes, Proc. Staff Meet., Mayo Clin. **15**:565-573 (Sept. 4) 1940.

normal dogs tolerated 0.25 unit of insulin per kilogram of body weight, whereas the same amount of insulin caused hypoglycemia and severe convulsions in adrenalectomized dogs. If large doses of adrenal cortical extract were administered to adrenalectomized dogs in the course of the twelve hours before the injection of insulin, hypoglycemia was less pronounced. Furthermore, it was demonstrated that insulin caused convulsions in adrenalectomized dogs before the concentration of blood sugar was reduced to the low level usually associated with symptoms of hypoglycemia. Treatment with cortical extract prevented these convulsions from occurring until the concentration of the blood sugar was at the level at which such convulsions ordinarily are expected.

Standard Dextrose Tolerance Tests: Thorn and his associates [42] demonstrated that patients who have Addison's disease tend to have a flat type of curve in response to the dextrose tolerance test when the sugar is given orally. This phenomenon, according to Thorn, appears to be the result of slow absorption of dextrose from the intestinal tract, a condition similar to that observed in cases of sprue. When dextrose was given intravenously the results in cases of Addison's disease did not differ significantly from the results in control cases except that in the former symptoms of hypoglycemia occurred more frequently in the third hour. The symptoms of hypoglycemia, which were often exceedingly severe, frequently occurred when the concentration of sugar in the blood was only moderately reduced. Spontaneous recovery was unusual. Treatment with adrenal cortical extract increased the fasting level of sugar in the blood, restored the dextrose tolerance curve to normal and prevented signs and symptoms of hypoglycemia. Similar changes with regard to the response to the dextrose tolerance test have been observed in adrenalectomized dogs.[47]

Intermediary Carbohydrate Metabolism: Suggestions based on some evidence have been advanced that adrenal cortical insufficiency is associated with a disturbance in the intermediate metabolism of carbohydrate. Reference [48] already has been made to the diminished stores of glycogen in the livers of adrenalectomized animals. Britton and Silvette [49] were unable to correct this depletion of glycogen in adrenalectomized cats by intraperitoneal injection of sodium lactate. Subsequently similar results

47. Kendall, E. C.; Flock, E. V.; Bollman, J. L., and Mann, F. C.: The Influence of Cortin and Sodium Chloride in Carbohydrate and Mineral Metabolism in Adrenalectomized Dogs, J. Biol. Chem. **126**:697-708 (Dec.) 1938. Lewis and others.[43b]

48. Britton and Silvette.[39] Long, Katzin and Fry.[40] Sprague.[41]

49. Britton, S. W., and Silvette, H.: On the Function of the Adrenal Cortex—General, Carbohydrate and Circulatory Theories, Am. J. Physiol. **107**:190-206 (Jan.) 1934.

were obtained for rats.[50] Similarly, the intravenous administration of racemic sodium lactate failed to relieve the hypoglycemic symptoms of adrenalectomized dogs [43b] and of a patient who had Addison's disease.[42] Diminished ability of adrenalectomized animals [43b] to convert lactic acid, pyruvic acid or the amino acid alanine (alphaaminopropionic acid) into dextrose has been observed in adrenalectomized, phlorhizinized rats. Failure to obtain the calculated amounts of dextrose in the urine after the administration of these potentially glycogenic substances is interpreted as a failure of formation of dextrose from these precursors.

Disturbances of Carbohydrate Metabolism in Cases of Addison's Disease: In contrast to observations on experimental animals, striking abnormalities of carbohydrate metabolism are rarely encountered in cases of Addison's disease. Anderson and Lyall [51] reported 1 case of atrophy of the adrenal glands in which fatal hypoglycemia occurred. They mentioned 2 instances of a similar episode recorded in the literature. Rushton and his associates [52] recently reported similar observations in another case of primary atrophy of the adrenal glands and were able to find an additional case in the literature. The occurrence in the literature of these few cases confirms the clinical impression that hypoglycemia is not a prominent feature of this condition. The fact cannot be ignored, however, that occasionally hypoglycemia with symptoms does occur in cases of Addison's disease.

Summary.—Enough evidence has been outlined to justify the original contention of Britton and Silvette [49] that in certain species of animals adrenal cortical insufficiency is associated with serious derangement of the metabolism of carbohydrate. This derangement has a definite pattern, characterized largely by (1) decreased rate of formation of dextrose from endogenous protein; (2) impaired synthesis of dextrose from a common precursor, such as lactic acid; (3) diminished supplies of glycogen in the liver and muscles, and (4) increased sensitivity to insulin. These disturbances vary among different species of animals. They can be corrected by injections of cortical extract or of some of the crystalline compounds which have been isolated from this extract.

How are these various abnormalities produced? What is their relation to the metabolism of "salt and water"? Why do they resemble

50. Buell, M. V.; Anderson, I. A., and Strauss, M. B.: On Carbohydrate Metabolism in Adrenalectomized Animals, Am. J. Physiol. **116**:274-281 (July) 1936.

51. Anderson, I. A., and Lyall, A.: Addison's Disease Due to Suprarenal Atrophy with Previous Thyrotoxicosis and Death from Hypoglycemia, Lancet **1**: 1039-1043 (May 1) 1937.

52. Rushton, J. G.; Cragg, R. W., and Stalker, L. K.: Spontaneous Hypoglycemia Due to Atrophy of the Adrenal Glands, Arch. Int. Med. **66**:531-540 (Sept.) 1940.

so closely the disturbances produced by removal of the anterior lobe of the hypophysis? At present one can only conjecture. For a more comprehensive treatment of this phase of the problem, the reader is referred to the excellent reviews [53] which have appeared recently.

ADRENAL CORTICAL SUBSTANCES

In the previous review,[1] mention was made of adrenal cortical extracts prepared by Rogoff and Stewart, by Hartman and his collaborators and by Swingle and Pfiffner, which were capable of supporting life in adrenalectomized animals. Since that time methods of preparation have improved. At present, potent extracts can be obtained from several pharmaceutic houses.[54] One of the great difficulties encountered in the preparation and standardization of these extracts has been the lack of suitable methods of assay. Numerous procedures, based on growth,[55] survival time,[56] prevention of muscular fatigue [57] and maintenance of normal concentrations of urea, electrolytes [58] and so forth in the blood,[59] have been advocated. Different methods of assay which test different physiologic activities often yield conflicting results, and as yet there is no unanimity of opinion as to which of these various procedures is most suitable.

Remarkable progress has been made in the isolation and identification of crystalline (steroid) compounds obtained from the adrenal cortex. Investigations have been carried on primarily by three groups

53. Soskin, S.: Metabolic Function of the Endocrine Glands, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Stanford University Press, 1941, vol. 3, pp. 543-572. Kendall, E. C.: The Adrenal Cortex, Arch. Path. **32**:474-501 (Sept.) 1941.

54. Loeb, R. F.: Conferences on Therapy: Treatment of Addison's Disease, J. A. M. A. **112**:2511-2516 (June 17) 1939.

55. Hartman, F. A., and Thorn, G. W.: A Biological Method for the Assay of Cortin, Proc. Soc. Exper. Biol. & Med. **28**:94-95 (Nov.) 1930.

56. Kutz, R. L.: A Method of Assay of Extracts Containing the Suprarenal Cortical Hormone, Proc. Soc. Exper. Biol. & Med. **29**:91-93 (Oct.) 1931.

57. Ingle, D. J.: Work Capacity of the Adrenalectomized Rat Treated with Cortin, Am. J. Physiol. **116**:622-625 (Aug.) 1936.

58. Harrop, G. A.; Pfiffner, J. J.; Weinstein, A., and Swingle, W. W.: A Biological Method of Assay of the Adrenal Cortical Hormone, Proc. Soc. Exper. Biol. & Med. **29**:449-451 (Jan.) 1932.

59. Pfiffner, J. J.; Swingle, W. W., and Vars, H. M.: The Cortical Hormone Requirement of the Adrenalectomized Dog, with Special Reference to a Method of Assay, J. Biol. Chem. **104**:701-716 (March) 1934. Harrop, G. A., and Thorn, G. W.: Studies on the Suprarenal Cortex: VI. The Effect of Suprarenal Cortical Hormone upon the Electrolyte Excretion of the Intact Normal Dog; a Proposed Method of Comparative Assay, J. Exper. Med. **65**:757-766 (June) 1937. Selye, H., and Schenker, V.: A Rapid and Sensitive Method for Bioassay of the Adrenalcortical Hormone, Proc. Soc. Exper. Biol. & Med. **39**:518-522 (Dec.) 1938.

of workers, namely, Reichstein and his associates, in Zurich, Switzerland; Wintersteiner and Pfiffner, at Columbia University, and Kendall, Mason and associates, at the Mayo Foundation. Although a great many compounds which are closely related in chemical structure to progesterone (fig. 4) have been isolated, only a few appear to have significant physiologic activity.[60] Furthermore, according to Wells and Kendall,[61] the total activity of the compounds represents only a small fraction of

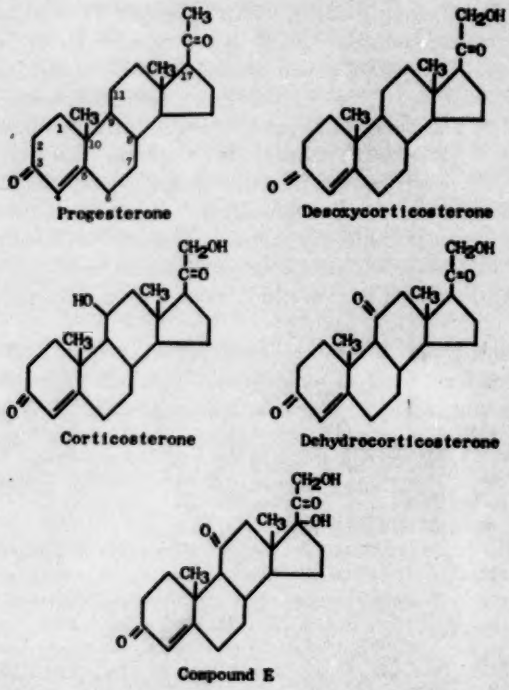

Fig. 4.—The structural similarity of some of the active compounds isolated from the adrenal cortex to progesterone.

the activity of the crude extract. For example, after removal of these crystalline substances from the crude extract, an unidentified amorphous

60. Mason, H. L.: Chemistry of the Adrenal Cortical Hormone, Endocrinology **25**:405-412 (Sept.) 1939.

61. Wells, B. B., and Kendall, E. C.: A Qualitative Difference in the Effect of Compounds Separated from the Adrenal Cortex on Distribution of Electrolytes and on Atrophy of the Adrenal and Thymus Glands of Rats, Proc. Staff Meet., Mayo Clin. **15**:133-139 (Feb. 28) 1940.

material still remains which retains 90 per cent of the potency of the original material as far as the maintenance of a normal electrolyte pattern in adrenalectomized dogs is concerned.

Desoxycorticosterone.—Clinically, the most important compound is desoxycorticosterone. This substance was first synthesized by Reichstein, who subsequently isolated it from extracts of the adrenal cortex. It is dispensed as desoxycorticosterone acetate dissolved in a vegetable oil and as yet is the only one of the compounds available for clinical use in a synthetic form. This substance causes retention of sodium and chloride and augments the excretion of potassium and phosphorus.[62] In cases of Addison's disease it increases the volume of plasma, rectifies the abnormal electrolyte pattern of the plasma and raises the blood pressure. After its administration the patient has a sense of well-being and his general condition improves. When large amounts of desoxycorticosterone acetate are administered excessive retention of sodium and chloride occurs, the stores of potassium are depleted and the blood volume increases above normal limits.[63] Rarely the concentration of sodium in the plasma remains subnormal, even though the level of potassium in the plasma is reduced. In contrast to this marked effect on electrolyte metabolism, desoxycorticosterone seems to have only a slight effect on carbohydrate metabolism.

Corticosterone, Dehydrocorticosterone and 17-Hydroxy-11-dehydrocorticosterone (Compound E of Kendall; Compound F of Pfiffner and Wintersteiner).—These three compounds isolated from the adrenal

62. (*a*) Thorn, G. W., and Eisenberg, H.: Stndies on Desoxy-Corticosterone, Endocrinology **25**:39-46 (July) 1939. (*b*) Thorn, G. W.; Engel, L. W., and Eisenberg, H.: The Effect of Corticosterone and Related Compounds on the Renal Excretion of Electrolytes, J. Exper. Med. **68**:161-172 (Aug.) 1938. (*c*) Simpson, S. L.: The Use of Desoxycorticosterone Acetate in Addison's Disease, Lancet **2**:557 (Sept. 3) 1938. (*d*) McCullagh, E. P.: Sodium and Chloride Retention in Addison's Disease Treated with Desoxycorticosterone Acetate, Cleveland Clin. Quart. **6**:105-108 (April) 1939. (*e*) Dryerre, H. W.: Effect of Desoxycorticosterone Acetate and Cortin on Salt Elimination in Addison's Disease, Brit. M. J. **1**:971-973 (May 13) 1939. (*f*) Thorn, G. W.; Howard, R. P., and Emerson, K., Jr.: Treatment of Addison's Disease with Desoxy-Corticosterone Acetate, a Synthetic Adrenal Cortical Hormone, J. Clin. Investigation **18**:449-467 (July) 1939. (*g*) Cleghorn, R. A.; Fowler, J. L. A., and Wenzel, J. S.: The Treatment of Addison's Disease by a Synthetic Adrenal Cortical Hormone (Desoxycorticosterone Acetate), Canad. M. A. J. **41**:226-231 (Sept.) 1939. (*h*) Ferrebee, J. W.; Ragan, C.; Atchley, D. W., and Loeb, R. F.: Desoxycorticosterone Esters: Certain Effects in the Treatment of Addison's Disease, J. A. M. A. **113**:1725-1731 (Nov. 4) 1939.

63. (*a*) Willson, D. M.; Rynearson, E. H., and Dry, T. J.: Cardiac Failure Following Treatment of Addison's Disease with Desoxycorticosterone Acetate, Proc. Staff Meet., Mayo Clin. **16**:168-173 (March 12) 1941. (*b*) Ferrebee and others.[62h]

cortex have in common an oxygen atom attached to carbon atom 11 of the steroid nucleus. In contrast to the action of desoxycorticosterone, they exert a marked effect on carbohydrate metabolism.[64] After their administration the abnormalities of carbohydrate metabolism associated with experimental adrenal cortical insufficiency appear to be corrected. Glycogen is stored in the liver and hypoglycemia prevented. In addition, compound E (which of all these compounds appears to exert the greatest effect on carbohydrate metabolism) restores the ability of adrenalectomized rats to form dextrose from lactic, pyruvic and glycogenic amino acids. In contrast to these results, Hampton,[65] working with patients who had Addison's disease, was unable to demonstrate any effect of compound E on the hypoglycemic action of insulin.

In addition to their effect on carbohydrate metabolism, these substances exert some effect on the excretion of electrolytes in the adrenalectomized dog. This action is comparatively feeble, however, for 10 mg. of compound E or 2.5 mg. of dehydrocorticosterone is required to produce the same effect on the distribution of electrolytes in the adrenalectomized dog that can be produced by only 0.3 mg. of desoxycorticosterone acetate.[66]

Amorphous Fraction.—This substance is the highly active concentrate of extracts of the adrenal cortex which remains after removal of the crystalline fractions already described. According to Kendall,[66] it is exceedingly potent in its effects on electrolyte metabolism. Only 1 or 2 micrograms per kilogram of body weight is required to maintain normal electrolyte patterns in the plasma of adrenalectomized dogs. This dose is in decided contrast to the relatively large amount of desoxycorticosterone required to produce the same effect.

It is questioned whether the adrenal cortex elaborates[67] one substance which can be regarded as the vital hormone of the gland or whether it elaborates a number of hormones, each of which has its own specific effect. A similar question, as yet unanswered, has bedeviled students of the physiology of the anterior portion of the pituitary.

DIAGNOSIS OF ADDISON'S DISEASE

Until comparatively recently, the recognition or exclusion of Addison's disease was based entirely on clinical evidence. In recent years

64. Long, Katzin and Fry.[40] Wells.[44] Lewis and others.[43b] Thorn and others.[42]

65. Hampton, H. P.: Personal communication to the authors.

66. Kendall, E. C.: Glandular Physiology and Therapy: The Function of the Adrenal Cortex, J. A. M. A. **116**:2394-2398 (May 24) 1941.

67. Kendall, E. C.: The Function of the Adrenal Cortex, Proc. Staff Meet., Mayo Clin. **15**:297-304 (May 8) 1940; Hormones, in Luck, J. M., and Smith, J. H. C.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1941, vol. 10, pp. 285-336.

several test procedures, however, have been developed which aid considerably in the evaluation of the functional integrity of the adrenal cortex. Among the earliest of these was that suggested by Harrop and associates,[68] which consisted simply of restricting the dietary intake of sodium chloride. If typical clinical symptoms of addisonian crisis ensued, the patient probably had Addison's disease. This procedure was decidedly hazardous to the patient if he did happen to have Addison's disease. At least 2 deaths have been reported after its use.[69] It also had the great disadvantage of not giving information that was decisively measurable, and the physician still had to rely largely on his clinical judgment as to what constituted a crisis.

In 1938 Cutler, Power and Wilder [70] modified and standardized the procedure of Harrop so that the concentration of chlorides in the urine could be utilized for diagnostic purposes. According to their method, the patient receives a standardized quantity of sodium chloride and potassium in the diet. In addition, potassium citrate and water are given in amounts proportional to the body weight. At the end of the fifty-two hours the test is terminated, and the urine voided in the last four hours is analyzed for its concentration of chloride. Under these conditions, patients who have adrenal cortical insufficiency excrete urine in which high concentrations of chloride and sodium are present. A high degree of diagnostic accuracy can be achieved by this method,[71] but the procedure has a number of disadvantages. Considerable time is required; careful chemical determinations are necessary, and it is somewhat haz-

68. Harrop, G. A.; Weinstein, A.; Soffer, L. J., and Trescher, J. H.: The Diagnosis and Treatment of Addison's Disease, J. A. M. A. **100**:1850-1855 (June 10) 1933.

69. Lilienfield, A.: The Use of the Low Salt Diet in the Diagnosis of Addison's Disease, J. A. M. A. **110**:804-805 (March 12) 1938. Garvin, C. F., and Reichle, H. S.: Death Presumably Due to the Use of the Salt Restriction Test in the Diagnosis of Addison's Disease, Ann. Int. Med. **14**:323-324 (Aug.) 1940.

70. Cutler, H. H.; Power, M. H., and Wilder, R. M.: Concentrations of Sodium, Chloride, and Potassium in the Blood Plasma and Urine of Patients with Addison's Disease: Their Diagnostic Significance, Proc. Staff Meet., Mayo Clin. **13**:244-249 (April 20) 1938; Concentrations of Chloride, Sodium, and Potassium in Urine and Blood: Their Diagnostic Significance in Adrenal Insufficiency, J. A. M. A. **111**:117-122 (July 9) 1938.

71. McCullagh, E. P., and Ryan, E. J.: The Use of Desoxycorticosterone Acetate in Addison's Disease, J. A. M. A. **114**:2530-2537 (June 29) 1940. Dryerre, H. W.: Addison's Disease: The Diagnostic Significance of the Sodium and Chloride Content of the Blood and Urine, Edinburgh M. J. **46**:267-277 (April) 1939. Thorn, G. W., and Firor, W. M.: Desoxycorticosterone Acetate Therapy in Addison's Disease: Clinical Considerations, J. A. M. A. **114**:2517-2525 (June 29) 1940. Stephens, D. J.: Pituitary and Adrenocortical Insufficiency: The Use of Sodium Chloride in the Treatment of Hypopituitarism, J. Clin. Endocrinol. **1**:109-112 (Feb.) 1941. Thorn, G. W.; Howard, R. P., and Dayman, H.: Electrolyte Changes in Pulmonary Tuberculosis, with Special Reference to Adrenal Cortical Function, Bull. Johns Hopkins Hosp. **67**:345-364 (Nov.) 1940.

ardous to the patient who has Addison's disease. In actual practice, in about half of the cases in which the test was performed at the Mayo Clinic it was not possible to complete it because of the occurrence of acute adrenal insufficiency.[72]

Robinson, Power and one of us (E. J. K.)[73] recently developed two closely related procedures which eliminated these difficulties in the majority of instances. The first one is based on a fact not generally appreciated, that after ingestion of large amounts of water patients who have Addison's disease do not experience normal prompt diuresis. This procedure is used primarily to exclude the adrenal cortex as the cause of fatigue states, hypotension, neurasthenia and similar disorders. Since potent adrenal cortical compounds have been made available to members of the medical profession the number of patients with such conditions suspected of having Addison's disease and treated accordingly has greatly increased. Obviously, a simple method of proving that adrenal cortical insufficiency is not the specific cause of the symptoms in these cases is highly desirable. The second procedure continues where the first leaves off. It is essentially chemical in character and is used to establish the diagnosis if the results of the first test indicate that the patient probably has Addison's disease. It has the great advantage of being safe, comparatively simple, rapid and reasonably decisive.

The two tests are conducted in the following manner: The day before the test the patient eats his usual three meals but omits extra salt. After 6 p. m. he does not eat or drink. At 10:30 p. m. he voids and discards the urine. All urine voided from 10:30 p. m. until and including 7:30 a. m. is collected, measured and saved for chemical analysis if this proves to be necessary. At 8:30 a. m. the patient voids again (if possible) and discards the urine. Immediately thereafter he is given 20 cc. of water per kilogram of body weight, or 9 cc. per pound, in the course of forty-five minutes. He is asked to void at 9:30, 10:30 and 11:30 a. m. and 12:30 p. m. Each of the specimens is measured. At 11:30 a. m. or 12:30 p. m. (the exact time is inconsequential) blood is drawn under oil for chemical analysis if the necessity for such studies appears likely, as by this time the results of this first procedure usually will be apparent.

The first procedure is concluded by comparing the volume of urine voided during the night with the volume of the largest single hourly specimen voided between 8:30 a. m. and 12:30 p. m.; the second procedure, by analyzing the urine voided during the night and the blood for

72. Willson, D. M.; Robinson, F. J.; Power, M. H., and Wilder, R. M.: The Diagnosis of Adrenal Cortical Insufficiency: Further Experience with the Cutler-Power-Wilder Salt Restriction Test, Arch. Int. Med., to be published.

73. Robinson, F. J.; Power, M. H., and Kepler, E. J.: Two New Procedures to Assist in the Recognition and Exclusion of Addison's Disease: A Preliminary Report, Proc. Staff Meet., Mayo Clin. **16**:577-583 (Sept. 10) 1941.

the concentrations of urea and chloride. A ratio is calculated from the values obtained in these four determinations.

From a study of 90 patients (40 of whom were proved by salt deprivation and by the Cutler, Power and Wilder procedure to have Addison's disease) it was ascertained that if the volume of urine which was voided during the night was less in amount than the volume of urine voided at any one hour during the morning, the patient did not have Addison's disease. If, on the other hand, the volume of urine voided during the night was greater than the volume voided at any one hour during the morning, the patient might or might not have Addison's disease, and the chemical analyses which constitute the second procedure were necessary. Under the latter circumstance the following ratio is calculated from the results of the four chemical determinations:

$$A = \frac{\text{Urea in urine (mg./100 cc.)}}{\text{Urea in plasma (mg./100 cc.)}} \times \frac{\text{Chloride in plasma (mg./100 cc.)}}{\text{Chloride in urine (mg./100 cc.)}} \times \frac{\text{Volume of day urine (cc.)}^{74}}{\text{Volume of night urine (cc.)}}$$

In nearly all instances in which the value for A did not exceed 25 the patient was found to have Addison's disease. Values for A of more than 30 indicated the absence of Addison's disease. The only exceptions encountered occurred in cases of nephritis. In conjunction with clinical evidence, the procedure proved to be decisively diagnostic in cases in which the presence of Addison's disease was proved by other methods.

Diagnostic methods which depend on the response of patients to specific treatment for Addison's disease have been developed by Thorn and his associates.[75] To be of value these procedures must be conducted under carefully controlled conditions. The use of mere subjective improvement following specific treatment in the absence of positive chemical data is an unreliable diagnostic criterion. Similarly, the tolerance of patients to the ingestion of potassium has been recommended as a diagnostic aid.[76] Recent reports,[77] however, indicate that this method is not wholly reliable.

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74. The term "day urine" applies to the largest of the hourly specimens voided during the day and "night urine," to the entire amount which was voided from 10:30 p. m. to 7:30 a. m. It is immaterial how these values are expressed, provided the same unit is used throughout the equation. For example, if the concentration of chloride in the plasma is expressed as milligrams of chloride per hundred cubic centimeters of plasma, the concentration of chloride in the urine should be expressed in the same manner.

75. Thorn, G. W.; Garbutt, H. R.; Hitchcock, F. A., and Hartman, F. A.: The Effect of Cortin on the Sodium, Potassium, Chloride, Inorganic Phosphorus, and Total Nitrogen Balance in Normal Subjects and in Patients with Addison's Disease, Endocrinology **21**:202-212 (March) 1937.

76. Zwemer, R. L., and Truszkowski, R.: Factors Affecting Human Potassium Tolerance, Proc. Soc. Exper. Biol. & Med. **35**:424-426 (Dec.) 1936.

77. Greene, J. A.; Levine, H., and Johnston, G. W.: Is the Potassium Tolerance Curve of Value in the Diagnosis of Adrenal Cortical Insufficiency in Man? Endocrinology **27**:375-377 (Sept.) 1940.

In considering the problems associated with the diagnosis of Addison's disease, it is necessary to bear in mind the fact that none of the procedures mentioned deals with the anatomic status of the adrenal cortex. This structure appears to have large margins of safety; a considerable portion of cortical substance must be destroyed before adrenal cortical insufficiency will occur. Before this degree of destruction takes place, the disease probably is essentially asymptomatic (with the possible exception of pigmentation), and any test based on adrenal cortical function may yield indecisive results.

Finally, there is often no decisive way of distinguishing atrophy from tuberculosis of the adrenal cortex except by the presence of calcification of the adrenal regions as seen in roentgenograms. The absence of calcification, however, does not exclude tuberculosis of the adrenal cortex. The latter condition can be inferred if tuberculosis can be demonstrated elsewhere in the body.

TREATMENT OF ADDISON'S DISEASE

Treatment of uncomplicated Addison's disease is directed primarily toward correction of the disturbances in metabolism of water and of electrolytes. This can be accomplished either by the administration of sufficient sodium to compensate for the loss in the urine or by preventing this loss through administration of adrenal cortical substances. Generally, a combination of the two methods is used. The administration of 10 Gm. of sodium chloride in addition to that in the diet may be sufficient to control most of the symptoms of patients who have a mild form of this disease. Better results are obtained, however, if sodium chloride is supplemented[78] with sodium lactate, sodium citrate or sodium bicarbonate. Wilder and his associates[18] have shown that restriction of the intake of potassium facilitates treatment with sodium salts. In a review of the clinical course of illness of 110 patients having Addison's disease who were seen at the Mayo Clinic between 1933 and 1940, Hampton and one of us (E. J. K.)[79] discussed the results of different therapeutic regimens which were followed during this seven year period. It was apparent that the restriction of the intake of potassium together with the use of extra sodium chloride gave definitely better therapeutic results than when the intake of potassium was unrestricted.

Until recently the only adrenal cortical substances which were available for clinical use were various commercial adrenal cortical extracts. Although these extracts vary considerably in potency, they have one common property: that is, large amounts can be administered with comparative safety. The optimal dose varies with the intake of electrolytes and has to be determined in a given case chiefly by trial and error.

78. Footnotes 10 *a* and *b*.

79. Hampton, H. P., and Kepler, E. J.: Addison's Disease: Treatment and Prognosis, Am. J. M. Sc. **202**:264-271 (Aug.) 1941.

Thompson [80] frequently administered from 10 to 30 cc. daily [81] and much larger amounts in isolated instances. Most physicians, however, employed smaller doses. Because patients found that the cost of treatment was burdensome or prohibitive, there was a tendency to use the least possible amount of extract that would prevent frank crisis. The patient's margin of safety, therefore, was narrow, and in spite of the combined treatment crises were relatively frequent. Overtreatment was practically unheard of. Occasionally a patient noted dependent edema, but usually this was of no great consequence.

In 1939 desoxycorticosterone was introduced for clinical use. Shortly thereafter [82] résumés of excellent therapeutic results were reported independently by a number of investigators. This substance decreases the excretion of sodium and increases the excretion of potassium. A rapid restoration both of the volume and of the chemical constituents of the blood and extracellular fluids follows.[83] These effects are augmented by increased intake of sodium and diminished by an increased intake of potassium. Desoxycorticosterone has the great advantage of being uniformly potent. In addition, the cost of its use, as measured by the expenditure of money required to rehabilitate the patient, is considerably less than that of most cortical extracts. On the other hand, like insulin and thyroxine, it has the great disadvantage of being a double-edged weapon. Only a short time after its introduction reports began to appear which demonstrated that overdosage was dangerous, and sometimes fatal.[84] Usually the chief symptoms of overdosage were those that might be expected from theoretic considerations, namely, hypertension, cardiac embarrassment and edema of varying degree. Even massive anasarca has been reported. The chemical changes in the plasma may be the antithesis of those which occur in adrenal cortical insufficiency. There were also reports of sudden death attributed to use of desoxycorticosterone which occurred when the patient seemingly was getting along satisfactorily. These were often attributed, usually for want of a better explanation, to hypoglycemia.[85] In addition to these

80. Thompson, W. O.; Thompson, P. K.; Taylor, S. G., III, and Hoffman, W. S.: The Treatment of Addison's Disease with Adrenal Cortex Extract, Endocrinology **24**:774-797 (June) 1939.

81. Thompson, W. O.: Therapeutic Symposium: Discussion, J. Clin. Endocrinol. **1**:83-84 (Jan.) 1941.

82. Wilder, R. M.: Progress in Treatment of Addison's Disease, Proc. Staff Meet., Mayo Clin. **15**:273-277 (May 1) 1940.

83. (*a*) Thorn, G. W.: Adrenal Cortical Hormone Therapy, Am. J. M. Sc. **197**:718-729 (May) 1939. (*b*) Footnote 62 *c*, *d*, *e* and *f*.

84. Ferrebee and others.[62b] Willson, Rynearson and Dry.[63a] Wilder.[82] Thorn.[83a]

85. Sudden death frequently occurred in cases of Addison's disease prior to the introduction of any form of replacement therapy. There is a strong temptation to attribute these deaths to hypoglycemia. The available evidence, however, does not warrant this assumption.

practical considerations, desoxycorticosterone acetate has the theoretic disadvantage of failing to correct all the abnormalities which are observed during experimental cortical insufficiency. In other words, its administration does not constitute complete replacement therapy.[86] However, in many instances, when the drug is used properly, it is difficult to demonstrate the residual symptoms which might be expected if the therapy were not reasonably complete.

The administration of desoxycorticosterone acetate does not eliminate the necessity for the controlled intake of electrolytes. Of these sodium is the most important. No hard and fast rules have been formulated as to the optimal amount of table salt which should be added to the diet. In determining the dose of desoxycorticosterone acetate, common sense suggests that the intake of sodium chloride should be kept constant while the dose of the drug is being varied. The intake of potassium is less important, provided that it is adequate in amount. Loeb and his associates [87] found that the concentration of potassium in the serum both of men and of dogs could be reduced to abnormally low values by administration of desoxycorticosterone acetate and restriction of the intake of potassium. Furthermore, Tooke, Power and one of us (E. J. K.)[88] showed that patients treated with desoxycorticosterone acetate could tolerate relatively large amounts of potassium. It appears, therefore, that the low potassium, high sodium intake which proved so useful in the treatment of patients having Addison's disease before the advent of desoxycorticosterone acetate is not only unnecessary but actually dangerous when this drug is being administered.

The use of desoxycorticosterone acetate, therefore, greatly intensifies a problem which has been present ever since replacement therapy was first used in the treatment of Addison's disease, namely, that of evaluating response to treatment. Unfortunately, no satisfactory and comparatively simple single criterion (comparable, for example, to urinalysis for sugar or the determination of the basal metabolic rate) has been developed by which response to therapy can be determined with certainty. Various indirect procedures have been advocated. Among these are determination of venous blood pressure, roentgenologic determination of the size of the heart, electrocardiographic study, measurement of

86. Gordon, E. S.: The Use of Desoxycorticosterone and Its Esters in the Treatment of Addison's Disease, J. A. M. A. **114**:2549-2551 (June 29) 1940. Kendall.[66] Thompson.[81]

87. Kuhlmann, D.; Ragan, C.; Ferrebee, J. W.; Atchley, D. W., and Loeb, R. F.: Toxic Effect of Desoxycorticosterone Esters in Dogs, Science **90**:496-497 (Nov. 24) 1939. Ferrebee and others.[62h]

88. Tooke, T. B., Jr.; Power, M. H., and Kepler, E. J.: The Tolerance of Patients Suffering from Addison's Disease to Potassium While Such Patients Are Being Treated with Desoxycorticosterone Acetate, Proc. Staff Meet., Mayo Clin. **15**:365-368 (May 1) 1940.

pulmonary vital capacity, hematocrit reading of the blood, measurement of the volume of blood and of extracellular fluid and chemical determination of plasma electrolytes. All of these appear to be either uncertain or too complex, or both, and their multiplicity testifies to their inadequacy. Most physicians who decide to use this drug for the treatment of Addison's disease, therefore, will have to be guided by such factors as sense of well-being, weight, blood pressure and the presence or absence of edema. As a general rule, it appears advisable to limit the dose to the least amount that is necessary to establish a sense of well-being. In this connection it should be emphasized that the intensity of Addison's disease, like that of many endocrine disorders, varies greatly in different patients and in the same patient at different times. Tuberculosis of the adrenal glands slowly advances from the medulla to the cortex. Islets of healthy tissue may remain, proliferate and even become adenomatous. Less is known about cortical atrophy, but it, too, probably progresses slowly. In either case and in any event the severity of disease is a variable. Consequently, even though the majority of patients have a fairly uniform response to a given dose of desoxycorticosterone acetate, an occasional patient fails to exhibit the expected degree of clinical improvement, while others readily show signs and symptoms of overtreatment. Furthermore, although the biochemical results of overtreatment are practically the antithesis of those of undertreatment, yet at times the clinical pictures of these two conditions may, confusingly enough, present in common such symptoms as weakness, nausea and vomiting.[63] Fortunately, however, such signs as an elevated venous pressure (grossly determined by the distance above the heart at which the peripheral veins collapse), subcutaneous edema, cardiac enlargement or hypertension,[89] which all point toward excessive accumulation of extracellular fluids, make for realization that too much desoxycorticosterone acetate or sodium or not enough potassium has been given. In short, the therapeutic effects of desoxycorticosterone acetate depend on the dose, the intake of potassium, the intake of sodium and the patient himself. Signs of overtreatment consequently may occur as the result of variations in any of these four factors, even though the actual dose of desoxycorticosterone did not appear to be particularly excessive. Occasionally patients are seen in a state of extreme cardiac embarrassment because of overtreatment. This represents as grave a medical emergency as the crisis of insufficiency. Its management con-

89. An apparently benign and asymptomatic type of essential hypertension may develop and persist without evidence of overtreatment. This type of hypertension is not directly related to increase in volume of extracellular fluid. (Roth, G. M.; Robinson, F. J., and Wilder, R. M.: Response of the Blood Pressure to the Cold Pressor Test in Addison's Disease During Treatment with Desoxycorticosterone Acetate, J. A. M. A. **116**:2429-2430 [May 24] 1941).

sists of those measures which remove the excess sodium, chloride and water from the body and relieve the strain on the circulatory system, that is, phlebotomy and the administration of mercurial diuretics, oxygen and digitalis.

The usual method of administering desoxycorticosterone acetate is by subcutaneous or intramuscular injection of the crystalline material dissolved in oil. As yet no case of serious infection resulting from the injection of this oily solution has been reported, nor has the incidence of hypersensitivity to the oily vehicle been a problem. The usual dose has been 1.5 to 5 mg. per day,[90] although some workers have obtained good results with considerably higher doses. Pellets of desoxycorticosterone acetate implanted subcutaneously have been shown by Thorn and his associates [91] to be effective in supplying the patient having Addison's disease with a continuous source of desoxycorticosterone acetate. This has both the theoretic advantage of simulating the more or less continuous secretion of the adrenal gland and the practical advantage of eliminating for the most part daily injections. Some cases have been reported in which the clinical response to desoxycorticosterone acetate in the form of implanted pellets was better than the response to daily parenteral administration. Before implantation of pellets of desoxycorticosterone acetate is undertaken, the necessary daily dose of desoxycorticosterone acetate should be determined accurately. Observations should be of sufficient duration to determine any decrease in the patient's required dose or any symptoms of overtreatment which might not become manifest until several weeks of treatment had elapsed. The effectiveness of a given amount of desoxycorticosterone acetate implanted obviously depends, too, on the speed with which the pellets dissolve. Rate of dissolution is dependent on such physical characteristics as compactness, shape and size. Use of pellets is still in the experimental stage.

A more recently developed method of administration of desoxycorticosterone acetate, which has many of the advantages derived from implantation of pellets, is the oral administration of the crystalline material dissolved in propylene glycol.[92] This solution is preferably administered sublingually several times a day. The dose varies roughly from one

90. Thorn, G. W.: Treatment of Addison's Disease, J. Clin. Endocrinol. **1**:76-81 (Jan.) 1941.

91. Thorn, G. W.; Howard, R. P.; Emerson, K., Jr., and Firor, W. M.: Treatment of Addison's Disease with Pellets of Crystalline Adrenal Cortical Hormone (Synthetic Desoxy-Corticocosterone Acetate): Implanted Subcutaneously, Bull. Johns Hopkins Hosp. **64**:339-365 (May) 1939.

92. Anderson, E.; Haymaker, W., and Henderson, E.: Successful Sublingual Therapy in Addison's Disease, J. A. M. A. **115**:2167-2168 (Dec. 21) 1940. Turnoff, D., and Rowntree, L. G.: Successful Sublingual Therapy in Addison's Disease, ibid. **116**:2016 (May 3) 1941.

and a half to five times the parenteral dose.[93] Since absorption of desoxycorticosterone from the oral route is less certain than that from the parenteral route, oral administration had best not be depended on during acute illness, especially when gastrointestinal disturbances are present.

For the treatment of acute adrenal insufficiency most writers agree that the administration of cortical extract is preferable to the use of desoxycorticosterone acetate. The extract may be given intravenously in amounts varying from 30 to 100 cc.

COMMENT

In this review we have devoted our attention chiefly to what is known about Addison's disease. What is not known is of equal importance; for example, the fundamental modus operandi of the adrenal cortical substances still remains a mystery. The site of their action is still debatable. The connecting link between the disruption of electrolyte metabolism, on the one hand, and the abnormalities of carbohydrate metabolism, on the other, has yet to be demonstrated. These are only a few of the obvious gaps in present day knowledge.

93. Hampton, H. P., and Kepler, E. J.: Addison's Disease: Treatment and Prognosis, Am. J. M. Sc. **202**:264-271 (Aug.) 1941.

DISEASES OF THE ADRENAL GLANDS

II. TUMORS OF THE ADRENAL CORTEX, DISEASES OF THE ADRENAL MEDULLA AND ALLIED DISTURBANCES

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Adrenal cortical tumors and allied disturbances [1] continue to arouse considerable interest. Since the last review of the subject appeared in this journal [2] a considerable number of cases have been reported and several comprehensive articles dealing with these conditions have appeared.[3]

TUMORS OF THE ADRENAL CORTEX

It is surprising, however, to find that no one has catalogued the symptoms as they have been described in the reports of cases which have been published. We have felt for a long time that some such work should be undertaken, because the various individual cases do not always conform, by any means, to the composite picture which has been so frequently described. Furthermore, there has been a tendency to use the "classic" case as the basis for endocrine hypotheses and implications which are not limited to this particular subject, but which bear on other

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1. This group of conditions is frequently discussed under the term adrenogenital syndrome, with the implication that there is a pathologic mechanism which is common to the group.

2. Kepler, E. J.: Diseases of the Adrenal Glands: A Review with Special Reference to the Clinical Aspects, Arch. Int. Med. **56**:105-135 (July) 1935.

3. (*a*) Grollman, A.: The Adrenals, Baltimore, Williams & Wilkins Company, 1936. (*b*) Haymaker, W., and Anderson, E.: Syndrome Arising from Hyperfunction of Adrenal Cortex: Adrenogenital and Cushing's Syndromes—A Review, Internat. Clin. **4**:244-299 (Dec.) 1938. (*c*) Kepler, E. J.: Tumors of the Suprarenal Cortex, Basophilic Tumors of the Pituitary Body, and Allied Diseases, in Philadelphia, F. A. Davis Company, 1939. (*d*) Kessel, F. K.: Morbus Piersol, G. W., and Bortz, E. L.: Cyclopedia of Medicine, Surgery and Specialties, Cushing: Ein Überblick über Klinik und Kasuistik des basophilem Hypophysenadenoms, Ergebn. d. inn. Med. u. Kinderh. **50**:620-678, 1936. (*e*) Wintersteiner, O.: Glandular Physiology and Therapy: The Adrenogenital Syndrome, J. A. M. A. **116**:2679-2683 (June 14) 1941. (*f*) Pico Estrada, O. M.: El diagnóstico de los tumores suprarrenales, Buenos Aires, El Ateneo, 1940.

current endocrinologic problems as well. With these thoughts in mind, we therefore reviewed all cases which we were able to find. The remarks which follow deal with some of the impressions that were obtained from this study.

To orient the reader who has not been particularly interested in this subject, it is necessary to point out that the various clinical syndromes which have been found to be associated with adrenal cortical tumor are conditioned by the sex of the patient and the period in the life history of the patient during which the tumor exerts its hormonal-like influences. Thus, the clinical picture differs among infants, boys, girls, men and women. In addition to those symptoms which are related to the sexual sphere, a group which may be called "metabolic," or "general," occur in varying degrees among persons of both sexes; they are not dependent on age and are essentially the same as those which occur in cases of Cushing's disease.[4] It appears plausible that the variations in the differentiation and maturity of the neoplastic cells may be factors of importance responsible for the variations in the clinical pictures which are encountered among persons of the same sex of comparable ages. Goormaghtigh,[5] for example, demonstrated cytologic and histologic differences in two tumors. One occurred in a feminized man, the other in a virilized woman. He was able to correlate these differences with assays of androgens and estrogens in the urine.

Reports[6] of cases in which endocrine symptoms are minimal or absent continue to appear, although in some instances it is difficult to be

4. Considerable confusion has arisen because of the terms "Cushing's syndrome" and "Cushing's disease." In this paper we have adopted the suggestion of Kessel and have applied the term "Cushing's syndrome" to the clinical picture described by Cushing under the term pituitary basophilism and the term "Cushing's disease" to the condition in which this clinical picture is associated with a basophilic adenoma of the anterior lobe of the hypophysis.

5. Goormaghtigh, N.: The Cytology of Functioning Adrenal Cortex Tumors, Am. J. Cancer **38**:32-40 (Jan.) 1940.

6. (*a*) Bocca, C. R.: Eléphantiasis nostras et tumeur de la surrénal, Lyon méd. **158**:402-407 (Oct. 11) 1936. (*b*) Eliason, E. L.: Cortical Adrenal Tumors, Internat. Clin. **2**:221-229 (June) 1938. (*c*) Fernblatt, H. M., and Alkert, B.: Adenoma, Adenocarcinoma of the Adrenals, Based on a Series of Thirty-Four Cases, New York State J. Med. **37**:861-864 (May 1) 1937. (*d*) McGavack, T. H.: Masculinizing and Non-Masculinizing Carcinomata of the Cortex of the Adrenal Gland: Report of Six Adult Cases, Endocrinology **26**:396-408 (March) 1940. (*e*) Carcinoma of Adrenal, Cabot Case 23121, New England J. Med. **216**:519-521 (March 25) 1937. (*f*) Nettrour, W. S.: Angioma of the Liver with Adenocarcinoma of the Suprarenal Gland: Report of Two Cases, Proc. Staff Meet., Mayo Clin. **11**:710-713 (Nov. 4) 1936. (*g*) Puig, R.: Corticosurrénalome malin avec

(Footnote continued on next page)

certain on the basis of published data that the adrenal cortex represented the primary source of the neoplasm.[6e] There is no question, however, that apparently "functionless" adrenal cortical neoplasms do occur. Some of these tumors, both with and without endocrine symptoms, have been highly malignant, rapidly growing neoplasms with a tendency to invade the renal veins and the vena cava and to metastasize to the liver and lungs.[7] Others have been relatively benign and encapsulated. In this connection the large number of adrenal cortical adenomas which are encountered accidentally in the course of routine necropsy is significant. In such instances there usually has not been any evidence during life that endocrine disease was present.

General, or Metabolic, Symptoms.—Among the symptoms which are unrelated to the age and sex of the patient and which occur among patients suffering either from Cushing's disease or from adrenal cortical tumor are the following: obesity or a change in the distribution of fat; hypertension; osteoporosis; purplish striations of the skin; acne; polycythemia; diabetes or changes in carbohydrate metabolism, and fatigue. In addition, there may be present in cases of adrenal cortical tumor those local and generalized phenomena which might occur as the result of any expanding malignant and metastasizing intra-abdominal mass. All these "general" symptoms are variable; any or all of them have been absent, and almost every combination of them has been found in individual instances.

Extreme obesity has not been encountered frequently in cases of proved adrenal cortical tumor. Exceptions occur, of which an example is the case of an infant recently reported by Marks, Thomas and Warkany.[8] Gain in weight, however, is a common symptom, and even when actual increase in weight has not occurred there may be a change in the distribution of adipose tissue. Marks and his associates [8] investigated the occurrence of obesity among 24 children who had adrenal cortical tumor as reported in the literature. They stated: "In spite of their monstrous appearance the actual weight of the children with tumors of the adrenal cortex may not be much greater than the average."

In the classic case, the obesity is confined to the face, trunk and abdomen. The extremities remain thin. The full moonlike face, the

métastases multiples et fièvre ondulante, Bull. et mém. Soc. méd. d. hôp. de Paris **53**:194-197 (Feb. 22) 1937. (*h*) Ravoire, J., and Guibert, H. L.: Adénome cortical d'une capsule surrénale (Etude anatomo-clinique), Ann. d'anat. path. **16**: 234-239 (Feb.) 1939. (*i*) Shenstone, N. S., and Lougheed, G. W.: Primary Cortical Carcinoma of the Suprarenal, Canad. M. A. J. **34**:188-189 (Feb.) 1936.

7. Wu, S. D.: Carcinoma of Adrenal Cortex, Chinese M. J. (supp.) **3**:52-93 (March) 1940.

8. Marks, T. M.; Thomas, J. M., and Warkany, J.: Adrenocortical Obesity in Children, Am. J. Dis. Child. **60**:923-942 (Oct.) 1940.

pad of fat high in the dorsal region and the other changes which occur in the distribution of fat produce a characteristic habitus. By no means all patients conform to this standard pattern. In the case reported by French[9] the patient was emaciated; in that recorded by Lightwood[10] the patient, although wasted, retained conspicuous deposits of fat about the face and chest. Two patients that we have seen had full faces but otherwise were not obese. Several instances have been reported in which no change in weight was apparent.

An increase in blood pressure occurred in many cases of adrenal cortical tumor. Both the systolic and the diastolic pressure were affected. This symptom appears to occur as frequently among children as among adult persons. In the case reported by Mainzer,[11] death resulted at the age of 8½ years, from a cerebrovascular accident that occurred after prolonged and severe hypertension. In some instances in which hypertension was marked the appearance of the ocular fundi was not unlike that in cases of essential hypertension. On the other hand, a number of cases have been reported in which hypertension was either minimal or absent.

Osteoporosis with pseudofractures (Looser's zones) occurs fairly commonly. Actual pathologic fractures have even been found. Because osteoporosis has been absent in many cases of adrenal cortical tumor, some authors have concluded erroneously that the presence of osteoporosis is diagnostic of Cushing's disease and that the possibility of adrenal cortical tumor could be excluded on this basis.

Striking abnormalities in the skin frequently have been associated with adrenal cortical tumor. In many instances the skin of the entire body became mottled, with unusual dusky purplish red areas, somewhat similar to those seen in cases of cutis marmorata or livedo racemosa. This mottling was most noticeable in the extremities and was designated as cyanosis in many of the published reports. The face usually was less mottled and its color more uniformly high than that of the rest of the body and sometimes resembled that seen in cases of polycythaemia vera. Acne was one of the most frequently mentioned of all the symptoms. It varied in severity from a few comedones to an intense eruption involving all the body except the abdomen and extremities and simulated the severe pustular types, such as acne cachecticorum, acne aggregata seu conglobata and pyoderma faciale. One of the most impressive of the abnormalities which accompany adrenal cortical tumor has been the purplish

9. French, H.: An Index of Differential Diagnosis of Main Symptoms by Various Writers, ed. 3, New York, William Wood & Company, 1922, p. 408.

10. Lightwood, R.: Tumour of the Suprarenal Cortex in an Infant of Eighteen Weeks, Arch. Dis. Childhood **7**:35-42, 1932.

11. Mainzer, F.: Nebennierenrindensyndrom mit arterieller Hypertension, Acta med. Scandinav. **87**:50-64, 1935.

striae atrophicae. These were noted chiefly on the abdomen, buttocks, thighs and arms. They may be 1 cm. or more in width and 10 cm. or more in length, tend to be depressed below the level of the rest of the skin and often are roughly parallel. They are apparently not to be attributed to changes in the weight of the patient or to stretching of the skin, because they have been encountered in instances in which the skin could not possibly have been stretched by a gain in weight. In a few reported cases the striae became infected. Ecchymoses, petechiae and hemorrhagic areas have been noted in some cases and extensive areas of keratosis pilaris in others. Recently, Albright and his associates [12] suggested that the changes observed in the skin are to be ascribed to a "thinning" produced by depletion of protein. We have difficulty in agreeing with this explanation.

Frank diabetes has not occurred as commonly as might be expected from the recent experimental work which indicates a close relation between the adrenal cortex and the metabolism of carbohydrates. However, minor disturbances in carbohydrate metabolism, such as alterations in the shape of the dextrose tolerance curve, frequently have been encountered. Lukens, Flippen and Thigpen [13] reviewed data concerning carbohydrate metabolism in 44 cases of adrenal cortical tumor and 11 cases of bilateral adrenal cortical hyperplasia reported between 1917 and 1935. No impairment of carbohydrate metabolism was noted in 24 cases of tumor and in 4 cases of hyperplasia. Impaired carbohydrate utilization, as measured by dextrose tolerance, occurred without glycosuria in 3 cases of tumor. Transitory glycosuria accompanied tumor in 4 cases and hyperplasia in 1 case, and marked glycosuria was encountered in 13 cases of tumor and in 6 cases of hyperplasia. Wilder and one of us (E. J. K.),[14] in 1938, reported a study of the carbohydrate metabolism of 8 patients suffering from adrenal cortical tumor. Definite diabetes was present in 1 instance and abnormal carbohydrate metabolism in 4 others. Shepardson and Shapiro,[15] in 1939, could find only 17 cases which they were willing to accept as proved instances of adrenal

12. Albright, F.; Parson, W., and Bloomberg, E.: Cushing's Syndrome Interpreted as Hyperadrenocorticism Leading to Hypergluconeogenesis: Results of Treatment with Testosterone Propionate, J. Clin. Endocrinol. **1**:375-384 (May) 1941.

13. Lukens, F. D. W.; Flippen, H. F., and Thigpen, F. M.: Adrenal Cortical Adenoma with Absence of the Opposite Adrenal, Am. J. M. Sc. **193**:812-820 (June) 1937.

14. Kepler, E. J., and Wilder, R. M.: Disturbances of Carbohydrate Metabolism Observed in Association with Tumors of the Adrenal Cortex, Acta med. Scandinav. **90**:87-96, 1938.

15. Shepardson, H. C., and Shapiro, E.: The Diabetes of Bearded Women (Suprarenal Tumor, Diabetes and Hirsutism), Endocrinology **24**:237-252 (Feb.) 1939.

cortical tumor associated with diabetes; to this number they added a case of their own. They emphasized that diabetes occurs only occasionally in the presence of adrenal cortical tumor and presented evidence for the concept that the adrenal cortex cannot be regarded as solely responsible for the imbalance of carbohydrate metabolism in cases of adrenal cortical tumor with diabetes. These authors concluded: "It seems probable, however, that the anlage of diabetes must be present in those patients who develop the Achard-Thiers symptom-complex."[16] We are inclined to concur with this concept of the relation between adrenal cortical tumor and diabetes.

Josephson[17] reported the case of a 43 year old woman who had hirsutism, osteoporosis and severe diabetes. Subsequently the diabetes disappeared and Addison's disease supervened. Four months later severe diabetes reappeared. An adrenal cortical tumor was surgically removed, but the patient died of acute adrenal cortical insufficiency after the operation. Sprague[18] recently observed a patient in whom severe diabetes, at times requiring the administration of more than 100 units of insulin daily for control, disappeared completely after removal of a huge adrenal cortical tumor. No other endocrine symptoms were observed in this patient. To our knowledge, this is the first instance in which diabetes has been the sole symptom of adrenal cortical tumor.

A number of authors have observed polycythemia of varying degree in association with adrenal cortical tumor. In the case of a patient we recently observed study of the blood by a hematologist disclosed all the characteristics of polycythaemia vera. In passing, it is worthy to note that the cause of the petechiae and hemorrhagic tendencies encountered among some patients with adrenal cortical tumor remains a mystery.

Among the less significant symptoms which have been noted are fatigue and pain. Pain has been at times a misleading symptom because it has occurred on the side opposite that on which the tumor is located. Backache and nerve root pains that result from osteoporosis have tended to confuse interpretation of the distress of which some of the patients complain. Finally, in cases in which the condition is of long standing or in cases in which there has been a rapidly growing or metastasizing tumor, such symptoms as abdominal mass, anemia and cachexia may be present.

Symptoms Related to the Age and Sex of the Patient.—The growth of a child afflicted with a tumor of the adrenal cortex is likely at first to

16. Diabetes of bearded women. The term has been used so loosely that it has ceased to have a precise meaning. In this particular case the term probably is synonymous with the "adrenogenital syndrome."

17. Josephson, B.: A Case of Alternating Cushing's Syndrome and Cachexia, Nord. med. tidskr. **16**:1396-1401, 1938.

18. Sprague, R.: Personal communication to the authors.

be unduly rapid. The long bones increase in length, and the so-called bone age is advanced.[19] Premature dentition has likewise been noted.[19a] These changes are not characteristic of adrenal neoplasms but, as Gross [19b] has pointed out, regularly accompany precocious sexual development caused by various endocrine disturbances.

Should the process continue long enough and precocious puberty take place, as has been the case, the epiphyses tend to ossify, the growth of the long bones ceases and the trunk continues to elongate. The result may be a dwarf with relatively short arms and legs and a skeletal framework somewhat suggestive of that of an achondroplastic dwarf. One such patient has been observed at the Mayo Clinic.[20] The nonspecific character of these changes is illustrated by Sacchi's [21] case, in which the deformity just described accompanied pubertas praecox associated with an interstitial cell tumor of the testis.

Among girls heterologous pubertas praecox seems to be the rule. When this occurs puberty not only is premature but is more or less masculine. In spite of the predominance of masculine features, instances have been reported in which menstruation has occurred. Although it has been asserted that premature menstruation does not occur among girls who have adrenal cortical tumor, vaginal and presumably uterine bleeding was noted in at least 4 instances.[22]

In most instances, when a young girl was affected by an adrenal cortical tumor, hair appeared on the pubes and subsequently on the face, thighs and the rest of the body. Sometimes the labia changed to the adult type. The clitoris usually hypertrophied. This hypertrophy was in some cases so excessive that it ultimately caused the clitoris to resemble a small penis.[23] In addition, in some instances the voice became deep and coarse, so that it resembled that of an adolescent boy.

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19. (*a*) Fraser, I.: Precocious Puberty in a Boy of One Year, Brit. J. Surg. **27**:521-526 (Jan.) 1940. (*b*) Gross, R. E.: Neoplasms Producing Endocrine Disturbances in Childhood, Am. J. Dis. Child. **59**:579-628 (March) 1940.

20. The photograph of this patient was published in a previous article (Kepler, E. J., and Rynearson, E. H.: Diseases of the Adrenal Glands, M. Clin. North America **24**:1035-1056 [July] 1940).

21. Sacchi, E., cited by Weber.[23g]

22. Bullock, W., and Sequeira, J. H.: On the Relation of the Suprarenal Capsules to the Sexual Organs, Tr. Path. Soc. London **56**:189-208, 1905. Cecil, H. L.: Hypertension, Obesity, Virilism and Pseudohermaphroditism as Caused by Suprarenal Tumors, J. A. M. A. **100**:463-466 (Feb. 18) 1933. Kepler, E. J.; Kennedy, R. L. J., and Davis, A. C.: Suprarenocortical Syndrome and Pituitary Basophilism: Presentation of Three New Cases, Proc. Staff Meet., Mayo Clin. **9**:169-182 (March 21) 1934. Kepler, E. J.; Walters, W., and Dixon, R. K.: Menstruation in a Child Aged Nineteen Months as the Result of Tumor of the Left Adrenal Cortex: Successful Surgical Treatment, ibid. **13**:362-366 (June 8) 1938.

23. Kreutzer, R.; Visillac, V. O.; Rivarola, J. E., and Vergnolles, M.: Consideraciones sobre un caso de síndrome interrenal, Prensa méd. argent. **24**:2306-2313 (Dec. 1) 1937.

Adrenal cortical tumor is a rarity among children of either sex. In 1939 Reilly, Lisser and Hinman [24] were able to collect from the literature only 40 cases in which the patients were girls.

Adrenal cortical tumors occur even less frequently among boys; to date we have knowledge of only 17 reported cases,[25] in 14 of which pathologic specimens were obtained either at necropsy or at operation. In the boys pubertas praecox was homologous; that is, puberty was essentially normal but premature. Usually hair appeared on the face, genitalia and body and the genitalia were enlarged. In some instances they attained adult size or were larger, and functioned accordingly. For example, spermatogenesis was noted in the cases reported by Lisser [25l] and Linser.[25k] Sexual function certainly occurred in the case described by Mainzer,[11] for the patient, a boy 8½ years old, was treated for acquired venereal infection. In the case reported by Josephson,[25i] on the other hand, the patient had infantile genitalia, childish features and no pubic or axillary hair. The photographs which accompanied the

24. Reilly, W. A.; Lisser, H., and Hinman, F.: Pseudosexual-Precocity and the Adrenal Cortical Syndrome in Preadolescent Girls: Report of a Case, Endocrinology **24**:91-114 (Jan.) 1939.

25. (*a*) Adams, C. E.: A Case of Precocious Development Associated with a Tumor of the Left Suprarenal Body, Tr. Path. Soc. London **56**:208-212 (April) 1905. (*b*) Baldwin, J. F.: Adrenal Precocity: Precocious Development of the External Genitals Due to Hypernephroma of the Adrenal Cortex, J. A. M. A. **63**:2286-2287 (Dec. 26) 1914. (*c*) Broster, L. R., and Vines, H. W. C.: The Adrenal Cortex: A Surgical and Pathological Study, London, H. K. Lewis & Co., Ltd., 1933. (*d*) Estiu, M., and Laborde, F. J.: Síndrome de hiper-interrenalismo en un niño, Rev. Asoc. méd. argent. **44**:423-426 (July-Aug.) 1931. (*e*) Fordyce, A. D., and Evans, W. H.: Suprarenal Virilism, with a Report of Two Cases: Pathological Notes, Quart. J. Med. **22**:557-563 (July) 1929. (*f*) Gordon, M. B., and Browder, E. J.: Suprarenal Carcinoma with Pubertas Praecox in a Boy Three Years of Age, Endocrinology **11**:265-278 (July-Aug.) 1927. (*g*) Guthrie, L., and Emery, W. d'E.: Precocious Obesity, Premature Sexual and Physical Development, and Hirsuties in Relation to Hypernephroma and Other Morbid Conditions, Tr. Clin. Soc. London **40**:175-202, 1907. (*h*) Harwood, J.: Right Hemihypertrophy and Pubertas Praecox, Proc. Roy. Soc. Med. **25**:951-958 (May) 1932. (*i*) Josephson, B.: The Adrenal Cortical Syndrome in a Case with Tumor from an Accessory Adrenal Gland, Acta med. Scandinav. **90**:385-396, 1936. (*j*) von Kup, J.: Ein neurer Beitrag zur Frage des Zusammenhanges zwischen Zirbel und Nebennierenrinde, Beitr. z. path. Anat. u. z. allg. Path. **100**:137-148, 1937. (*k*) Linser, P.: Ueber die Beziehungen zwischen Nebennieren und Körperwachstum, besonders Riesenwuchs, Beitr. z. klin. Chir. **37**:282-305, 1903. (*l*) Lisser, H.: Successful Removal of Adrenal Cortical Tumor Causing Sexual Precocity in a Boy Five Years of Age, Tr. A. Am. Physicians **48**:224-235, 1933. (*m*) Rowntree, L. G., and Ball, R. G.: Diseases of the Suprarenal Glands, Endocrinology **17**:263-294 (May-June) 1933. (*n*) Tschernobrow, E.: Ueber eine Geschwulst der Nebenniere bei einem 11-jährigen Knaben mit frühzeitiger Geschlechtsentwicklung, Thesis, Zurich, 1919. (*o*) Lightwood.[10] (*p*) Mainzer.[11] (*q*) Fraser.[19a]

report of this case suggest a curious combination of Fröhlich's and Cushing's syndromes.

In the great majority of recently reported cases of adrenal cortical tumor the patients were young women. The clinical picture usually was similar to that which occurs among girls before the age of puberty. The chief endocrine symptoms noted were amenorrhea, hirsutism of the male type, enlargement of the clitoris and development of a masculine habitus, with atrophy of the breasts and coarsening of the voice. Homosexual tendencies, loss of libido and loss of the distinctly feminine psychic characteristics occasionally have been reported.

We found a variation in the number and magnitude of these symptoms. In several instances, including 1 which we encountered at the Mayo Clinic,[26] amenorrhea was the only endocrine symptom present. On the other hand, in a case in which the condition was of fairly long standing, the woman was almost completely virilized. The case reported by Lukens and Palmer [27] is an example of complete virilism with none of the stigmas of Cushing's syndrome. In certain other cases the end result presented all the clinical characteristics of Cushing's syndrome, with no changes suggestive of reversal of sex. A patient with such characteristics recently was observed by us. The great majority of cases reported were distributed between these extremes, and all conceivable gradations between the extremes were represented.

Only a few cases have been reported in which the patient was an adult male. The reports which have received the most attention are those in which feminization occurred.[28] The most recent example of this group is the case reported by Levy Simpson and Joll [28c] in 1938. Their patient was a 34 year old physician in whom the enlargement of the

26. Walters, W.; Wilder, R. M., and Kepler, E. J.: The Suprarenal Cortical Syndrome with Presentation of Ten Cases, Ann. Surg. **100**:670-688 (Oct.) 1934.

27. Lukens, F. D. W., and Palmer, H. D.: Adrenal Cortical Virilism, Endocrinology **26**:941-945 (June) 1940.

28. (*a*) Bittorf, A.: Nebennierentumor und Geschlechtsdrüsenausfall beim Manne, Berl. klin. Wchnschr. **56**:776 (Aug. 18) 1919. (*b*) Holl, G.: Zwei männliche Fälle von Nebennierenrindentumoren mit innersekretorischen Störungen, Deutsche Ztschr. f. Chir. **226**:277-295 (July) 1930. (*c*) Levy Simpson, S., and Joll, C. A.: Feminization in a Male Adult with Carcinoma of the Adrenal Cortex, Endocrinology **22**:595-604 (May) 1938. (*d*) Lisser, H.: A Case of Adrenal Cortical Tumor in an Adult Male Causing Gynecomastia and Lactation, ibid. **20**: 567-569 (July) 1936. (*e*) Mathias, E.: Ueber Geschwülste der Nebennierenrinde mit morphogenetischen Wirkungen, Virchows Arch. f. path. Anat. **236**:446-469, 1922. (*f*) Volini, I. F., and O'Brien, G. F.: Pluriglandular Syndrome Associated with Carcinoma of Right Suprarenal Gland, M. Clin. North America **18**:1367-1376 (March) 1935. (*g*) Weber, F. P.: A Note on the Causation of Gynaecomastia (Mammary Feminism), Lancet **1**:1034-1035 (May 29) 1926. (*h*) zum Busch, J. P.: Gynäkomastie bei Hypernephrom, Deutsche med. Wchnschr. **53**:323 (Feb. 18) 1927.

breasts, loss of libido and potentia and regression in size of the sexual organs led to the discovery of an adrenal tumor. Some improvement followed removal of the neoplasm, but the patient died of metastasis two years later.

A number of instances have been reported among men, as among women, in which no endocrine symptoms whatever were associated with a neoplasm of the adrenal cortex.[29] The only symptoms present in such instances were those which might occur in the presence of any retroperitoneal mass adjacent to a kidney.

Elliott and Shallard[30] observed a man in whom the symptoms produced by an adrenal cortical carcinoma were those of Cushing's syndrome. Feminization did not occur.

Tenenbaum[31] described a 13 year old girl in whom generalized neurofibromatosis accompanied precocious puberty, hirsutism, weakness and moon face. Removal of an adrenal cortical tumor was followed by regression of all symptoms, including the neurofibromatosis, but the recurrence of symptoms eighteen months later presumably indicated recurrence of the tumor. This case is doubly interesting in that a number of instances have been reported in which generalized neurofibromatosis accompanied tumors of chromaffin tissue of the adrenal medulla (see "Diseases of the Adrenal Medulla").

Adrenal Cortical Hyperplasia.—Closely related both to tumor of the adrenal cortex and to Cushing's disease is a condition which frequently has been referred to as adrenal cortical "hyperplasia." Although the writings of Broster and others[32] a number of years ago aroused wide interest in this condition, recent literature has done little to clarify its significance. It is apparently neither a clinical nor a pathologic entity. So far as we can determine, the essential facts concerning it may be summarized as follows: At necropsy in an appreciable number of proved cases of Cushing's disease, the adrenal cortex has been found to be enlarged and presumably hyperplastic. In another group of cases in which the clinical picture is compatible with the diagnosis either of adrenal cortical tumor or of basophil adenoma of the pituitary body, hyperplasia of the adrenal cortex was the only macroscopic observation at necropsy. In a large number of instances in which exploration of the adrenal bodies was undertaken because of the presence of symptoms

29. Footnote 6 *c* and *i*.

30. Elliott, G. T., and Shallard, B. T.: Cushing's Syndrome, M. J. Australia **1**:390-393 (Feb. 26) 1938.

31. Tenenbaum, J.: Carcinoma of the Adrenal Cortex: Case Report, J. Urol. **42**:277-287 (Sept.) 1939.

32. Broster, L. R.: The Surgery of the Adrenal Cortex, Brit. J. Surg. **26**: 925-941 (April) 1939; The Differential Diagnosis of Cushing's Syndrome (Basophilism) of Pituitary or Adrenal Origin, Brit. M. J. **1**:425-428 (March 16) 1940. Broster and Vines.[25e]

indistinguishable from those usually associated with adrenal cortical tumor, the only finding has been "hyperplasia" of the adrenal cortex. Three cases have been reported [33] in which the patient appeared clinically to have Cushing's syndrome and at necropsy was found to have a thymic tumor and hyperplastic adrenal glands.[34] Furthermore, the association of adrenal cortical hyperplasia with feminine pseudohermaphrodism has been noted too frequently for the association to be regarded as a coincidence.[35] It does not appear justifiable at present to assume that this association necessarily implies a causal relation. Those interested in this controversial subject are referred to the papers of Cahill,[36] Young [37] and Grollman.[38] Finally, it should be mentioned that at necropsy the adrenal cortex is found to be enlarged and presumably hyperplastic in a number of diversified conditions in which endocrine symptoms were known to be absent during the life of the patient.

Wilkins and his associates [38] recently reported a remarkable case in which a 3½ year old boy had pubertas praecox, mental retardation and a pronounced craving for salt. He died as the result of what appeared clinically and chemically to be a state of acute adrenal cortical insufficiency. Necropsy disclosed marked adrenal cortical hyperplasia, with complete derangement of the normal cortical architecture and replacement of the normal constituents of the androgenic cells. The normal cellular structure of the testes was similarly disturbed by the presence of the same type of cells. This case lends important support to the early

33. (*a*) Kepler, E. J.: Report of Four Cases, in Symposium: Polyglandular Dyscrasias Involving Abnormalities of Sexual Characteristics, Proc. Staff Meet., Mayo Clin. **8**:102-107 (Feb. 15) 1933. (*b*) Leyton, O.; Turnbull, H. M., and Bratton, A. B.: Primary Cancer of the Thymus with Pluriglandular Disturbance, J. Path. & Bact. **34**:635-660, 1931.

34. There have been no additional cases of this syndrome reported since the last review in this journal.

35. Bosselman, H.: Intersex mit suprarenalem Virilismus (Knochenmarkentwicklung in dem hyperplastischen Nebennieren), Endokrinologie **19**:292-306 (Nov.) 1937. Miller, I. D., and Kenny, P. J.: A Case of Adrenal Cortical Hyperplasia, Associated with Pseudohermaphroditism, Brit. J. Surg. **27**:728-733 (April) 1940. von Neugebauer, cited by Lisser, H.: The Uni-Glandular Origin of Pleuriglandular Syndromes, Endokrinologie **5**:138-170 (Oct.) 1929.

36. Cahill, G. F.: Adrenogenital Syndrome and Adrenocortical Tumors, New England J. Med. **218**:803-815 (May 12) 1938.

37. Young, H. H.: Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases, Baltimore, Williams & Wilkins Company, 1937; Prostates in Females: Relation to Adrenal Cortical Hyperplasia, Tr. Am. A. Genito-Urin. Surgeons **30**:281-290, 1937.

38. Wilkins, L.; Fleischmann, W., and Howard, J. E.: Macrogenitosomia Praecox Associated with Hyperplasia of the Androgenic Tissue of the Adrenal and Death from Corticoadrenal Insufficiency: Case Report, Endocrinology **26**: 385-395 (March) 1940.

theories of Grollman [39] and others that the cells of the androgenic zone are distinct physiologically, as well as embryologically and cytologically. It would appear not only that the overgrowth of androgenic cells produced excessive quantities of virilizing substances but that the resultant derangement led to adrenal cortical insufficiency.

In recent years little light has been thrown on the problem of the large group of women who have varying degrees of hirsutism, which is sometimes associated with menstrual disturbances. Some of these women have a slightly masculine habitus. Others are obese. Still others appear to be entirely normal except that they are hairy. On the whole, such women are and appear to be healthy, and their problem is usually chiefly cosmetic. Except for the presence of hair they have few or none of the other symptoms of adrenal cortical tumor or Cushing's syndrome. They constitute a tragic and poorly understood group of patients. Some authors prefer to consider their condition as a form of adrenal cortical hyperplasia or "subclinical pituitary basophilism." [40] This concept recently has aroused wider interest, since it has been demonstrated that some of these women exhibit minor alterations in the urinary excretion of estrogens and androgens.[40] Notwithstanding, the histologic and physiologic bases for this assumption rest on exceedingly shaky foundations. It must still be admitted that practically nothing is known about the causation of the hirsutism of these patients. Incidentally, we have never seen beneficial results follow any form of therapy whatsoever. Mussio Fournier and associates [41] reported the case of a patient which is an exception to the rule.

A curious syndrome associated with hyperplasia of the adrenal glands recently has been described which appears to bear little relation to the clinical states that have been discussed. Di Ruggiero and Jolly,[42] in 1938, reported a case in which an infant died at the age of 4 weeks after persistent vomiting which simulated that of pyloric stenosis. The only observation at necropsy was pronounced adrenal hyperplasia ("chiefly medullary"). Dijkhuizen and Behr,[43] in 1940, reported 4 cases of a similar condition. In all cases an identical clinical picture was presented, with death occurring in the fourth to the sixth week after birth. In the 3 cases in which the results of necropsy were available, the only observation was tremendous hypertrophy of the adrenal glands (which weighed

39. Compare Wintersteiner's [3e] comments regarding Grollman's present position on this point.

40. Glass, S. J., and Bergman, H. C.: Subclinical Adrenogenital Syndrome, Endocrinology **23**:625-629 (Nov.) 1938.

41. Mussio Fournier, J. C.; Albrieux, A. S., and Morato Manaro, J.: Acción local de las hormonas, Arch. clín. e inst. de endocrinol. **1**:39-56, 1937-1940.

42. Di Ruggiero, and Jolly, A.: Vomissements graves du nourrisson et hypertrophie des surrénals, Ann. d'anat. path. **15**:332-335 (March) 1938.

43. Dijkhuizen, R. K., and Behr, E.: Adrenal Hypertrophy in Infants: A New Clinical Entity of the Neonatal Period, Acta pædiat. **27**:279-295, 1940.

24, 22 and 34 Gm., respectively). The authors reported that the entire gland was hypertrophic, particularly the cortex, with overgrowth of such magnitude as to throw the surface into folds suggesting the sulci and gyri of brain tissue. In 2 of the 4 cases the condition occurred in siblings, 1 of whom, a male, was a pseudohermaphrodite. One is reluctant to assume that in these cases the hyperplasia of the adrenal cortex was coincidental. However, specific evidence that the hyperplasia of the adrenal cortex was a cause of the clinical picture is lacking in the accompanying data.

Diagnosis.—In the last review [2] evidence was cited that Cushing's syndrome is not specific for Cushing's disease but may occur in association with a number of pathologic processes, among which is tumor of the adrenal cortex. Since that time this assertion has been amply documented by a large number of case reports. Because of this lack of specificity the major obstacle in the diagnosis of an adrenal cortical tumor is elimination of Cushing's disease. Conversely, in the diagnosis of Cushing's disease the chief concern of the diagnostician is exclusion of tumor of the adrenal cortex. The problem of treatment renders this question of differential diagnosis of great importance, for the results of treatment of Cushing's disease with roentgen rays are uncertain and often disappointing, whereas, by contrast, successful removal of adrenal cortical neoplasms has been followed by results which are among the most spectacular in medicine. There is a school of thought (see Bland and Goldstein [44]) which holds that unless there is unequivocal clinical evidence of an adrenal cortical tumor all patients who have Cushing's syndrome should receive roentgen ray therapy over the pituitary body because surgical exploration of the adrenal bodies is a great operative risk. Analysis of the reported cases, in our opinion, supports the opposite view: that in every case of a condition thought to be Cushing's disease, regardless of how typical it may seem, the patient should be examined with the suspicion in the physician's mind that the cause may be a surgically removable tumor of the adrenal gland.

Recent literature indicates widespread and generalized use of the procedure brought into favor by Cahill and associates,[45] in which the adrenal glands are delineated in roentgenograms by the injection of air into the perirenal fascial spaces.[46] In a considerable number of the

44. Bland, P. B., and Goldstein, L.: Pituitary Basophilism, Surg., Gynec. & Obst. **65**:644-656 (Nov.) 1937.

45. (*a*) Cahill, G. F.; Loeb, R. F.; Kurzrok, R.; Stout, A. P., and Smith, F. M.: Adrenal Cortical Tumors, Surg., Gynec. & Obst. **62**:287-313 (Feb. 15) 1936. (*b*) Cahill.[36]

46. (*a*) Hyman, A., and Wilhelm, S. F.: The Differential Diagnosis of Renal and Suprarenal Tumors, J. Urol. **40**:737-751 (Dec.) 1938. (*b*) Mencher, W. H.: Perirenal Insufflation, J. A. M. A. **109**:1338-1341 (Oct. 23) 1937. (*c*) Walters, W., and Kepler, E. J.: Surgical Lesions of the Adrenal Glands, ibid. **111**:1061-1065 (Sept. 17) 1938.

reported cases, evidence of adrenal tumor or of adrenal hyperplasia was obtained by this method when other methods gave negative results. Instances have been reported of collapse after perirenal insufflation (Hyman and Wilhelm),[46a] and in at least 1 instance the development of emphysema after the insufflation of air interfered with subsequent surgical procedures (Lukens, Flippen and Thigpen).[13] We have had little experience with this technic, but Cope and Schatzi[47] reported marked success and few untoward reactions in a large series of cases in which they employed a modification of Cahill's method. There seems to be little doubt that in the hands of careful and experienced surgeons the method is reasonably safe[47] and that it is capable of disclosing the presence not only of a gross lesion but of hyperplasia and small adrenal cortex adenoma. Negative results obtained by this method, however, cannot necessarily be regarded as conclusive.

In some centers—at the Mayo clinic, for example, surgical exploration remains the method of choice for determining the status of the adrenal glands. If the procedure is carried out by a competent surgeon the risk is slight, provided that both adrenal glands are not partially resected or damaged by rough handling. When the patient is a female, some surgeons still prefer to use an abdominal approach to visualize the ovaries at the same time. Others prefer a posterolumbar incision. The chief objection to the use of a major surgical procedure as a diagnostic aid is the fact that the patient may be greatly disappointed if a tumor is not found to account for his condition, even though such a possibility has been carefully and frankly stressed before the operation.

The most promising development in the diagnosis of hyperfunctioning lesions of the adrenal cortex in recent years has been the clinical application of assay of the urine for hormone-like substances. Earlier reports were concerned with biologic methods; more recent ones, with colorimetric determinations or chemical isolation of specific chemical compounds. The substances which have been investigated can be arranged in four categories: (1) estrogenic substances; (2) androgenic substances; (3) substances which prolong survival of adrenalectomized animals, and (4) inactive compounds related chemically to hormones. Excellent summaries of the literature pertaining to this subject have been published recently by Looney[48] and Wintersteiner.[3e]

Estrogenic Substances: Kurzrok, cited by Cahill and others,[43a] in 1930, found a large amount of estrogenic substance in the urine of a patient proved to have adrenal cortical tumor (case 2 of the series

47. Cope, O., and Schatzi, R.: Tumors of the Adrenal Glands: I. A Modified Air Injection Roentgen Technic for Demonstrating Cortical and Medullary Tumors, Arch. Int. Med. **64**:1222-1238 (Dec.) 1939.

48. Looney, J. M.: Sex Factors of the Adrenal Gland, Endocrinology **27**:511-520 (Sept.) 1940.

reported by Cahill and associates).[45a] Results of the Aschheim-Zondek test for pregnancy were negative. Five days after removal of the tumor there was complete absence of estrogen from the urine. Frank,[49] in 1934, was the first to propose that the excretion of estrogenic substances in the urine might be of diagnostic value in the presence of carcinoma of the adrenal cortex. He found enormous quantities of estrogen in the urine of 4 women who had hyperfunctioning adrenal cortical tumor. Other cases in which values for estrogens were high have been reported by Graef, Bunim and Rottino [50] and by Lukens and Palmer.[27] McGavack [6d] reported an increase in the urinary excretion of estrogens in a woman who had carcinoma of the adrenal cortex. He also reported normal values for estrogens and high values for androgens in the urine of a number of patients suffering from adrenal cortical hyperplasia.

Normal values for estrogen in the urine were found by Bruins Slot [51] in a woman who had a hyperfunctioning adrenal cortical tumor. Walters and one of us (E. J. K.) [52] were unable to demonstrate any increase in the excretion of estrogen in several of the cases in a series; in a case recently reported from the Massachusetts General Hospital, Boston,[53] only a slight elevation in the output of estrogen in the urine occurred.

Of particular interest are the determinations of estrogens in the urine of men in whom an adrenal cortical tumor is associated with evidences of feminization. Records of such cases are few, and in only 1, that reported by Levy Simpson and Joll in 1938,[23c] are results of estrogen assays included. The case has been referred to elsewhere in this review. This patient excreted large amounts of an estrogenic substance, presumably estrone, before operation; this substance disappeared with regression of the feminine characteristics following surgical removal of the tumor but reappeared later with recurrence of the neoplasm and its symptoms.

Glass and Bergman [40] reported 2 cases in which feminization in males (gynecomastia and genital atrophy) apparently was not associated with tumor, a circumstance which they ascribed to adrenal cortical hyper-

49. Frank, R. T.: Suggested Test for Functional Cortical Adrenal Tumor, Proc. Soc. Exper. Biol. & Med. **31**:1204-1206 (June) 1934; A Suggested Test for Cortical Adrenal Carcinoma, J. A. M. A. **109**:1121 (Oct. 2) 1937.

50. Graef, I.; Bunim, J. J., and Rottino, A.: Hirsutism, Hypertension and Obesity Associated with Carcinoma of the Adrenal Cortex: Indeterminate Pituitary Adenoma and Selective Changes in the Beta Cells (Basophils) of the Hypophysis, Arch. Int. Med. **57**:1085-1103 (June) 1936.

51. Bruins Slot, W. J.: The Relation of Sex Hormones in a Case of Virilism by Hypernephroma, Acta med. Scandinav. **89**:371-375, 1936.

52. Walters, W., and Kepler, E. J.: Adrenal Cortical Tumors and Their Treatment: A Study of Seven Operated Cases, Ann. Surg. **107**:881-898 (June) 1938.

53. Carcinoma of the Adrenal Cortex, Left with Metastases to Periaortic Nodes, Cabot Case 26261, New England J. Med. **222**:1086-1090 (June 27) 1940.

function. The androgen-estrogen ratio was definitely reduced in both these cases, in 1 because of an increased excretion of estrogens and in the other because of a diminished output of androgens.

Saphir and Parker [54] found an increased excretion of estrogens in a patient who presented the adrenogenital syndrome, with normal adrenal bodies and small nests of adrenal cortical cells in the ovaries. Lack of complete recovery after removal of the ovaries was attributed to the probable presence of similar nests elsewhere.

Androgenic Substances: The excretion in the urine of androgens by patients who exhibit symptoms suggestive of adrenal cortical hyperfunction has received more attention in recent years than has the excretion of estrogens. Koch [55] found an increase of the androgen-estrogen ratio of the urine in most, but not all, of the cases of virilism in his series; in most instances this was due not only to an increased output of androgens but to a decreased excretion of estrogens. Levy Simpson, de Fremery and Macbeth [56] found an excess of androgen in the urine of 4 of 7 women who had the adrenogenital syndrome, 3 women who had Cushing's syndrome and 2 of 3 girls who had pseudohermaphrodism. No excess of androgenic material was found in the urine of 3 women who had the adrenogenital syndrome, 1 woman more than 50 years old who had the Achard-Thiers syndrome and a pseudohermaphrodite 4 years old. Elevated values for the excretion of androgens in the urine have been noted by many authors, both for patients who have adrenal cortical tumor and for those in whom the same syndrome is associated with adrenal cortical hyperplasia. In some cases of tumor the excretion of androgens has been enormous. Dingemanse and Laqueur,[57] Callow [58] and Bruins Slot [51] all reported values exceeding 2,000 international units per day.

An important contribution recently has been made by Crooke and Callow.[59] These authors studied 4 patients suffering from Cushing's

54. Saphir, W., and Parker, M. L.: Adrenal Virilism, J. A. M. A. **107**:1287-1288 (Oct. 17) 1936.

55. Koch, F. C.: Recent Studies on the Excretion of Male Sex Hormones in Man, Ann. Int. Med. **11**:297-301 (Aug.) 1937; The Chemistry and Biology of Male Sex Hormones, in Harvey Lectures, 1937-1938, Baltimore, Williams & Wilkins Company, 1938.

56. Levy Simpson, S.; de Fremery, P., and Macbeth, A.: The Presence of an Excess of 'Male' (Comb-Growth and Prostate-Stimulating) Hormone in Virilism and Pseudo-Hermaphroditism, Endocrinology **20**:363-372 (May) 1936.

57. Dingemanse and Laqueur, E.: Occurrence of Abnormally Large Quantities of Male Hormones in Urine of Patients with Suprarenal Tumor, Nederl. tijdschr. v. geneesk. **82**:4166-4170 (Aug. 27) 1938.

58. Callow, R. K.: The Significance of the Excretion of Sex Hormones in the Urine, Proc. Roy. Soc. Med. **31**:841-856 (Feb. 8) 1938.

59. Crooke, A. C., and Callow, R. K.: The Differential Diagnosis of Forms of Basophilism (Cushing's Syndrome), Particularly by the Estimation of Urinary Androgens, Quart. J. Med. **8**:233-349 (July) 1939.

syndrome, 2 of whom were proved to have basophil adenoma of the pituitary body and 2 tumor of the adrenal cortex. The 2 patients who had adrenal cortical tumor both excreted large quantities of androgenic material in the urine, whereas the patients who had basophil adenoma of the pituitary body excreted normal amounts. Should further investigation in other cases confirm this distinction, the importance of the observation as a diagnostic aid is obvious. Drips and Osterberg,[60] however, found normal values for the output of androgens in the urine of 3 women who had Cushing's disease but an increased amount in the urine of a man who had the same condition. McGavack [60d] reported normal values for androgens in the urine of a woman found at operation to have carcinoma of the adrenal cortex, and Mason [61] likewise recorded normal values for androgens (5 micrograms per day) in the urine of a patient found to have adrenal cortical tumor.

Anderson, Haymaker and Joseph,[62] using extracts of the blood and urine of 3 patients who had Cushing's syndrome, were able to prolong the survival of adrenalectomized animals. Similar extracts obtained from normal controls produced no such effect. The authors expressed the belief that this demonstrated the presence of excessive quantities of the adrenal cortical hormone in the blood and urine of these patients. On critical examination, however, the data of these investigators are not entirely convincing.

An increasing number of specific compounds, among them cresols, triols, steroids and allied substances, not all of which have shown hormonal activity, have been isolated from the urine of patients suffering from adrenal cortical tumor.[63] Several of these substances had not

60. Drips, D. G., and Osterberg, A. E.: An Evaluation of a Colorimetric and a Biologic Method for Determining Urinary Androgens, Endocrinology **27**: 345-354 (Sept.) 1940.

61. Mason, H.: Personal communication to the authors.

62. Anderson, E., and Haymaker, W.: Adrenal Cortical Hormone (Cortin) in Blood and Urine of Patients with Cushing's Disease, Proc. Soc. Exper. Biol. & Med. **38**:610-613 (June) 1938. Anderson, E.; Haymaker, W., and Joseph, M.: Hormone and Electrolyte Studies of Patients with Hyperadrenocortical Syndrome (Cushing's Syndrome), Endocrinology **23**:398-402 (Oct.) 1938.

63. Burrows, H.; Cook, J. W.; Roe, E. M. F., and Warren, F. L.: Isolation of Δ: 3:5 Androstadiene-17-one from the Urine of a Man with a Malignant Tumor of the Adrenal Cortex, Biochem. J. **31**:950-961 (June) 1937. Butler, G. C., and Marrian, G. F.: The Isolation of Pregnane-3, 17, 20-Triol from the Urine of Women Showing Adrenogenital Syndrome, J. Biol. Chem. **119**:565-572 (July) 1937; Chemical Studies on the Adreno-Genital Syndrome: The Isolation of 3 (α)-Hydroxyetiocholane-17-one, 3 (β)-Hydroxyetioallicholane-17-one (Isoandrosterone) and a New Triol from the Urine of a Woman with an Adrenal Tumor, ibid. **124**:237-247 (June) 1938. Kenyon, A. T.; Gallagher, T. F.; Peterson, D. H.; Dortman, R. I., and Koch, F. C.: The Urinary Excretion of Androgenic and Estrogenic Substances in Certain Endocrine States: Studies in Hypogonadism, Gynecomastia and Virilism, J. Clin. Investigation **16**:705-717 (Sept.) 1937. Koch.[55] Callow.[58]

previously been found in tissue extracts. It seems reasonable to expect that further precise chemical recognition of the substances elaborated by adrenal cortical tumors offers the greatest likelihood of clarifying the pathologic physiology of this syndrome.

In summary, it would appear that some, but by no means all, patients who have adrenal cortical tumor excrete excessive quantities of estrogens. Many, but not all, patients suffering from adrenal cortical tumor excrete excessive quantities of "androgenic material." A few patients apparently excrete excessive quantities of both. A considerable variety of chemical compounds, some biologically active, others inert, have been isolated. Many of these have not been discovered in other material. In short, in cases of adrenal cortical tumor, the results of assays of urine for substances that possess hormonal properties have been about as variable as the clinical pictures encountered. These results are in keeping with the diversified histologic structure of adrenal cortical tumors. Nor are they surprising when one considers the histologic similarity, one to another, of cortical cells, luteal cells and the interstitial cells of the testes in conjunction with the chemical similarity of the various crystalline cortical steroids, the estrogens and the androgens.

As has been mentioned, adrenal cortical hyperplasia has in some instances been associated with clinical pictures which resemble in almost every detail those accompanying both adrenal cortical tumor and Cushing's disease. In such instances there is no means by which a positive differential diagnosis can be made except by direct surgical examination or by visualization of the hyperplastic cortex in roentgenograms after the insufflation of air.

In addition to the conditions which have been mentioned, the differential diagnosis of adrenal cortical tumor among children involves consideration of all the pathologic processes which result in sexual and somatic precocity. Among these are (1) various intracranial lesions (such as internal hydrocephalus,[64] pinealoma,[65] tumor of the third

64. Dorff, G. B., and Shapiro, L. M.: A Clinicopathologic Study of Sexual Precocity with Hydrocephalus: Report of Two Cases Occurring in Females, with Postmortem Examinations in One, Am. J. Dis. Child. **53**:481-499 (Feb.) 1937. Thomas, A., and Schaeffer, H.: Un cas de macrogénitosomie précoce avec hydrocéphalie, lésions inflammatoires de la région infundibulo-tubérienne et symphyse cervical triméningée, sans néoplasme intracranien, Rev. neurol. **2**:595-606 (Nov. 5) 1931.

65. Bailey, P., and Jelliffe, S. E.: Tumors of the Pineal Body, with an Account of the Pineal Syndrome, the Report of a Case of Teratoma of the Pineal and Abstracts of All Previously Recorded Cases of Pineal Tumors, Arch. Int. Med. **8**:851-880 (Dec.) 1911. von Frankl-Hochwart, L.: Ueber Diagnose der Zirbeldrüsentumoren, Deutsche Ztschr. f. Nervenh. **36-37**:455-465, 1909. Horrax, G.: Further Observations on Tumor of the Pineal Body, Arch. Neurol. & Psychiat. **35**:215-228 (Feb.) 1936. Horrax, G., and Bailey, P.: Tumors of the Pineal Body, ibid. **13**:423-470 (April) 1925.

ventricle [66] and similar lesions in the region of the pituitary body), (2) interstitial cell tumor of the testes [67] and (3) arrhenoblastoma and granulosa cell tumor of the ovary.[68] Among adult persons one must also consider thymoma associated with adrenal cortical hyperplasia and arrhenoblastoma and possibly lutein cell tumor (Saphir).[69] The diagnosis in all of these instances may be relatively easy if physical examination discloses the presence of the tumor. We were unable to find reports of any special diagnostic methods applicable to these problems which already have not been discussed.

Pathologic Physiology.—Except for what clarification has resulted from assays of hormonal-like substances in the urine, as previously discussed, knowledge of the pathologic physiology of adrenal cortical tumor has not been materially advanced in the past few years.

Some authors have become so impressed with the diverse manifestations of adrenal cortical tumors that they have hypothesized the existence of two syndromes associated with such neoplasms. For example, Haymaker and Anderson,[3b] in their recent review, suggested the term adrenogenital syndrome for the classic picture of adrenal virilism in which sexual alterations predominate and the term adrenocortical syndrome for the clinical picture of Cushing's syndrome. They suggested, incidentally, that the former probably represents excessive production by the adrenal cortex of an androgenic substance and the latter excessive production of the so-called essential, or vital, adrenal cortical hormone. Although it may be freely admitted that individual cases have been reported which serve as typical examples of the aforementioned extremes, the majority of cases fail to conform to such precise definition

66. Dods, L.: Adrenohypophyseal Dystrophies of Infancy and Childhood, M. J. Australia **2**:277-286 (Sept. 1) 1934. Heuyer, G.; Lhermitte, J.; de Martel, and Vogt, C.: Un cas de macrogénitosomie précoce liée à un épendymogliome de la région mamillo-tubérale, Rev. neurol. **2**:194-210, 1931. LeMarquand, H. S., and Russell, D. S.: A Case of Pubertas Praecox (Macrogenitosomia Praecox) in a Boy Associated with a Tumor in the Floor of the Third Ventricle, Roy. Berkshire Hosp. Rep., 1934-1935, pp. 31-61.

67. Stewart, C. A.; Bell, E. T., and Roehlke, A. B.: An Interstitial-Cell Tumor of the Testis with Hypergenitalism in a Child of Five Years, Am. J. Cancer **26**:144-150 (Jan.) 1936. Sacchi.[21] Weber.[28g]

68. Meyer, R.: The Pathology of Some Special Ovarian Tumors and Their Relation to Sex Characteristics, Am. J. Obst. & Gynec. **22**:697-713 (Nov.) 1931. Novak, E.: Masculinizing Tumors of the Ovary (Arrhenoblastoma, Adrenal Ovarian Tumors), with Report of Six Additional Cases of Arrhenoblastoma, ibid. **36**:840-858 (Nov.) 1938. Novak, E., and Gray, L. A.: Clinical and Pathologic Differentiation of Certain Special Ovarian Tumors: Granulosa Cell Carcinoma, Arrhenoblastoma, Disgerminoma, Brenner Tumor, ibid. **31**:213-229 (Feb.) 1936.

69. Saphir, O.: So-Called Lutein Cell Tumors, Am. J. Obst. & Gynec. **37**:1008-1014 (June) 1939.

and as a group embrace virtually every conceivable combination of symptoms. In fact, survey of the accumulated mass of reports of cases impresses the observer with the striking pleomorphic character of the clinical pictures which have been encountered.

In our judgment, theories regarding the mechanisms which are responsible for the production of the various clinical syndromes will be of little value until the physiologic relations of the adrenal cortex have been clarified. For the time being, therefore, the problem rests largely with the physiologist and the biochemist rather than with the clinician.

It is remarkable that so few instances of hyperfunctioning adrenal cortical lesions have been encountered in which alterations of electrolyte metabolism could be demonstrated. Loeb [45a] conducted chemical studies on many of Cahill's patients, with negative results, an experience shared by many investigators. The first instance in which changes in the electrolyte pattern of the blood were noted was reported by one of us (E. J. K.) [33a] in 1933, and a second instance was added a few years later.[70] In both cases pronounced alkalosis was associated with a high value for plasma bicarbonate and a low concentration of plasma chloride. In 1937 McQuarrie, Johnson and Ziegler [71] published the results of intensive metabolic studies in a case previously reported by Ulrich,[72] in which the diagnosis of basophil adenoma of the pituitary was confirmed at necropsy. Disturbances of the pattern of plasma electrolytes in this case were in most respects diametrically opposite those found in a case of typical Addison's disease. The most striking abnormalities were the high concentration of bicarbonate and sodium and the decrease in potassium and chloride, which produced a persistent tendency toward alkalosis, in addition to the clinical features characteristic of Cushing's syndrome.

Goldzieher [73] has also reported a high value for plasma sodium and a low value for plasma potassium in the case of a woman past the period of the menopause who exhibited the picture of Cushing's syndrome, presumably caused by adrenal cortical tumor. He did not mention the presence of alkalosis or values for bicarbonate.

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70. (*a*) Walters, W.; Wilder, R. M., and Kepler, E. J.: The Suprarenal Cortical Syndrome: Report of Two Cases, with Successful Surgical Treatment, Proc. Staff Meet., Mayo Clin. **9**:400-407 (July 3) 1934. (*b*) Kepler.[2]

71. McQuarrie, I.; Johnson, R. M., and Ziegler, M. R.: Plasma Electrolyte Disturbance in Patient with Hypercorticoadrenal Syndrome Contrasted with That Found in Addison's Disease, Endocrinology **21**:762-772 (Nov.) 1937.

72. Ulrich, H. L.: A Basophilic Adenoma of the Pituitary Gland, Minnesota Med. **18**:73-77 (Feb.) 1935.

73. Goldzieher, M. A.: Adrenal Cortical Disturbances, Internat. Clin. **4**:20-39 (Dec.) 1939.

Willson, Power and one of us (E. J. K.) [74] recently reported a similar case in which the patient had Cushing's syndrome, presumably associated with a basophil adenoma of the pituitary. In this case, the chief chemical findings were diminished concentration of potassium and chloride, increased concentration of bicarbonate and an elevated p_H (alkalosis).[75] The concentration of sodium in the plasma in this case was not elevated. It is remarkable not that such phenomena have been observed in these instances but that in all the cases of so-called hypercorticoadrenalism such changes have been noted so rarely. It is equally remarkable that among the few cases in which "hypercorticalism" has been associated with disturbances of electrolyte metabolism there is, to our knowledge, not a single instance of proved adrenal cortical tumor.

Treatment.—There is general agreement that the treatment of an adrenal cortical tumor is surgical. If a tumor can be completely removed, the result is spectacular improvement. Except in instances of tumor among children, in which precocious epiphysial union may occasionally have produced irreversible dwarfism, and in certain instances in which facial hair has persisted,[27] the disappearance of symptoms usually is complete after total removal of the tumor. If the tumor has penetrated its capsule, eventual recurrence, either locally or in the form of widespread metastasis, is to be anticipated.

The hazard of removal of an adrenal cortical tumor, as judged by reports of isolated cases, appears to be distressingly great. On the other hand, reports [76] of series of cases have appeared in which a much more favorable impression is conveyed.[77] In many instances death is still attributed to postoperative "shock." A critical analysis of the fatalities leads us to believe that, in spite of statements to the contrary, death more often than not is the result of the occurrence of acute adrenal insufficiency. It is well known that in many cases of tumor of one adrenal cortex the opposite adrenal gland is atrophic. Even complete absence of the opposite gland has been reported by Lukens and associates [18] and by

74. Willson, D. M.; Power, M. H., and Kepler, E. J.: Alkalosis and Low Plasma Potassium in Case of Cushing's Syndrome: Metabolic Study, J. Clin. Investigation **19**:701-707 (Sept.) 1940.

75. In 2 of the 3 cases at the Mayo Clinic the magnitude of the alkalosis was sufficient to produce tetany.

76. Walters, Wilder and Kepler, footnotes 26 and 70*a*. Cahill and others.[45a]

77. Fifteen patients suffering from adrenal cortical tumor have been operated on at the Mayo Clinic to date. The only operative fatality in the entire group occurred in 1924, prior to the advent of modern methods for the treatment of adrenal cortical insufficiency (Keyser, L. D., and Walters, W.: Carcinoma of the Suprarenal Associated with Unusual Endocrine Manifestations, J. A. M. A. **82**: 87-88 [Jan. 12] 1924).

Feinblatt.[78] It is highly probable, therefore, that the opposite gland frequently, if not always, is somewhat functionally inadequate.[79] Removal of a functioning tumor under such circumstances throws a tremendous burden on the opposite gland, comparable to that which occurs in cases of adrenal apoplexy. The physiologic upheaval may be even more marked than that which occurs in crises of Addison's disease, because of the fact that the organism has had no opportunity to become adjusted to a low level of adrenal cortical function. The general plan of preoperative and postoperative treatment has been outlined by Walters and one of us (E. J. K.).[52] It is based on the assumption that adrenal cortical insufficiency will occur after operation and should be prevented by treating the patient before the operation as if he had Addison's disease. If signs suggesting adrenal cortical insufficiency occur in spite of prophylactic treatment, vigorous therapy with adrenal cortical extract and a solution of sodium chloride is indicated. In this connection it is worth while to point out that although most, if not all, cortical extracts on the market vary in potency, they have one property in common; namely, enormous doses can be administered safely. (This statement does not apply to the synthetic compound desoxycorticosterone acetate.) A study of the reported cases in which death occurred after operation will convince any one that pusillanimous therapy is worthless under such circumstances.

A review of our own cases, as well as those which have been reported in the literature, indicates that imminent danger can be suspected after operation by a rapidly increasing temperature, a decreasing blood pressure, the clinical picture of "shock" and the chemical changes in the blood that accompany acute adrenal insufficiency. On theoretic grounds, the use of desoxycorticosterone acetate should constitute ideal preoperative and postoperative therapy. As yet no cases in which this substance has been employed for this particular purpose have been reported. We have used it, apparently with excellent results, in 1 instance in which a large malignant tumor of the adrenal cortex was successfully removed. This was not an ideal test case, because the only symptoms present were amenorrhea, hirsutism, an abdominal mass and a slight degree of rubicundity.

The treatment of hyperplasia of the adrenal cortex remains on a far less satisfactory basis than does that of adrenal cortical tumor. In some instances improvement has followed removal of one hypertrophic adrenal

78. Feinblatt, H. M.: Carcinoma of Cortex of Suprarenal Gland with Virilism, Arch. Int. Med. **38**:469-473 (Oct.) 1926.

79. We have gained the impression that this is especially true in cases in which there are marked metabolic abnormalities, as contrasted with cases in which there are virilizing phenomena.

gland or a portion of both hypertrophic adrenal glands, but usually the results have been relatively insignificant when compared with the phenomenal improvement which follows the removal of a tumor. When hyperplasia of the adrenal cortex is associated with a basophil adenoma of the pituitary body, irradiation of the latter at times has led to remarkable improvement, but on the whole the results of treatment of Cushing's disease have been most unhappy. Broster [32] remains the leading exponent of unilateral adrenalectomy when hyperplasia is found in association with virilism.

DISEASES OF THE ADRENAL MEDULLA

Lesions of the adrenal medulla continue to be encountered far less frequently than do those of the cortex. Most common is primary malignant tumor of the adrenal medulla, which does not produce endocrine symptoms. The wide latitude of the histologic variations in such tumors has given rise to a distressing and confusing lack of uniformity in nomenclature. The tumor arises from sympathetic ganglion cells or their derivatives and, according to the degree of cellular differentiation present, generally is designated by such terms as sympathogonioma, sympathoblastoma, neuroblastoma, neurocytoma or glioma.

Malignant tumor of the adrenal medulla usually is encountered during childhood; reports of cases in which it has been observed in an adult are few. Fingerland,[80] however, encountered such a tumor in a 71 year old man.

The number of cases in the literature has grown steadily. Scott and associates [81] in 1933 were able to collect 158 cases of the condition; Lewis and Geschichter [82] a year later added 40 more, in 7 of which the lesions had originated outside the adrenal gland. Redman, Agerty, Barthmaier and Fisher [83] in 1938 reviewed reports of 113 cases which had been published since the appearance of the review by Scott and his co-workers.

The symptoms of the tumor in the majority of cases are produced by metastasis, although there have been occasional exceptions to this sequence. When metastasis to the orbit and skull occurs the tumor is customarily classified as the Hutchison type, whereas in cases of

80. Fingerland, A.: Sur un cas de paragangliome, Bull. Assoc. franç. p. l'étude du cancer **25**:334-349 (Feb.) 1936.

81. Scott, E.; Oliver, M. G., and Oliver, M. H.: Sympathetic Tumors of the Adrenal Medulla with Report of Four Cases, Am. J. Cancer **17**:396-417, 1933.

82. Lewis, D., and Geschichter, C. F.: Tumors of the Sympathetic Nervous System: Neuroblastoma, Paraganglioma, Ganglioneuroma, Arch. Surg. **28**:16-58 (Jan.) 1934.

83. Redman, J. L.; Agerty, H. A.; Barthmaier, O. F., and Fisher, H. R.: Adrenal Neuroblastoma: Report of a Case and Review of the Literature, Am. J. Dis. Child. **56**:1097-1112 (Dec.) 1938.

metastasis to the liver, with ascites, the tumor is known as the Pepper type. Division into these types is obviously arbitrary, and close inspection of reported cases indicates that many of the lesions have had features of both. Kato and Wachter [84] analyzed 179 such neoplasms, of which 76 were of the Hutchison type, 57 were of the Pepper type and 2 were of the mixed type. The remaining 44 were impossible to classify. In 93 cases the tumor occurred in boys, in 73 cases it occurred in girls and in 13 cases the sex was not stated. The average age of the patients suffering from tumor of the Hutchison type was 3.9 years, and the average age of those suffering from tumor of the Pepper type was 1.7 years.

In a number of instances bizarre hematologic changes have added confusion to the diagnosis. Von Albertini and Willi [85] reported a case in which a neuroblastoma of the right adrenal body of the Hutchison type remained undiagnosed during the life of the patient, a girl 2½ years old, for whom studies of the blood and bone marrow had suggested leukemia.

Treatment of such lesions has rather obviously been hopeless, and to date no record has been encountered of any case in which the patient has survived for any length of time. Surgical treatment in most instances has been out of the question because of the obvious presence of metastasis. Malisoff [86] encountered a case which constituted a remarkable exception: A girl 14 years old had a tumor weighing 2,435 Gm. which was removed from one adrenal body.

Lake and Ayers [87] reported the recovery of a girl 3½ years old after irradiation of a neuroblastoma of the right adrenal body. The period of observation had been short.

Medullary Hyperadrenalism.—Medullary hyperadrenalism resulting from a hyperfunctioning tumor of the adrenal medulla or an allied tumor of the chromaffin tissue has been recognized as a clinical and pathologic entity for a relatively short time. The tumor generally is termed pheochromocytoma or paraganglioma. Usually it is encapsulated and benign and possesses most of the histologic characteristics of adult chromaffin cells.

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84. Kato, K., and Wachter, H. E.: Adrenal Sympathicoblastoma in Children, J. Pediat. **12**:449-462 (April) 1938.

85. von Albertini, A., and Willi, H.: Neuroblastoma Sympathicum der rechten Nebenniere mit Metastasierung nach dem Typhus Hutchison, Ann. pædiat. **152**: 129-159 (Dec.) 1938.

86. Malisoff, S.: Neuroblastoma of Adrenal Gland, J. Urol. **41**:296-302 (March) 1939.

87. Lake, W. F., and Ayers, A. J.: Renal and Perirenal Tumors in Children: Report of Two Cases, South. M. J. **31**:992-995 (Sept.) 1938.

Pheochromocytoma is an uncommon lesion. Brunschwig and Humphreys [88] reviewed the literature in 1939 and could find reports of only 103 cases of the neoplasm. Of these 103 tumors, 77 were unilateral, 13 were bilateral and 13 had occurred outside the adrenal body.

This tumor gives rise to a syndrome characterized by paroxysmal hypertension, vasomotor attacks, tachycardia, nausea, vomiting, tremor and, occasionally, glycosuria and elevation of the basal metabolic rate. The symptoms encountered obviously are those that might be expected to follow the sudden administration of an excess of epinephrine and may be exceedingly varied. Thorough summaries of the symptomatology have been published by Van Epps and associates [89] and Von Gärtner.[90]

A number of instances have been reported in which hypertension was continuous.[91] Sudden death, sometimes occurring during or after a minor surgical procedure, has been observed frequently.[92] In most cases in which this syndrome has been encountered, analysis of the tumor for the presence of epinephrine has yielded enormous quantities of this substance.[93] Attempts to demonstrate excessive quantities of epinephrine

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88. Brunschwig, A., and Humphreys, E.: Excision of Pheochromocytoma, J. A. M. A. **115**:355-357 (Aug. 3) 1940.

89. Van Epps, E. F.; Hyndman, O. R., and Greene, J. A.: Clinical Manifestations of Paroxysmal Hypertension Associated with Pheochromocytoma of the Adrenal Gland: Report of Two Cases, Arch. Int. Med. **65**:1123-1129 (June) 1940.

90. von Gärtner, W.: Das klinische Bild, insbesondere die Kreislaufstörungen bei Paragangliom der Nebenniere, Ztschr. f. Kreislaufforsch. **28**:82-90 (Feb.) 1936.

91. (*a*) Binger, M. W., and Craig, W. McK.: An Atypical Case of Hypertension with a Tumor of the Adrenal Gland, Proc. Staff Meet., Mayo Clin. **13**: 17-20 (Jan. 12) 1938. (*b*) Edward, D. G. F.: Pheochromocytomata and Hypertension with Details of a Case, J. Path. & Bact. **45**:391-403 (Sept.) 1937. (*c*) Hegglin, R., and Nabholz, H.: Das Nebennieremarksyndrom: Zur Kasuistik der chromaffinem Geschwülste, Ztschr. f. klin. Med. **134**:161-195 (May) 1938. (*d*) Palmer, R. S., and Castleman, B.: Paraganglioma (Chromaffinoma, Pheochromocytoma) of the Adrenal Gland Simulating Malignant Hypertension, New England J. Med. **219**:793-796 (Nov. 17) 1938. Van Epps, Hyndman and Greene.[89]

92. Wells, A. H., and Boman, P. G.: The Clinical and Pathologic Identity of Pheochromocytoma: Report of a Case, J. A. M. A. **109**:1176-1180 (Oct. 9) 1937.

93. (*a*) Belt, A. E., and Powell, T. O.: Clinical Manifestations of the Chromaffin Cell Tumors Arising from the Suprarenal Medulla, Surg., Gynec. & Obst. **59**:9-24 (July) 1934. (*b*) von Brenner, F.; Konzett, H., and Nagl, F.: Ueber ein Phäochromozytom der Nebenniere, München. med. Wchnschr. **85**:914-916 (June 17) 1938. (*c*) Fein, M. J., and Carmann, F. F.: Medullary Carcinoma of the Suprarenal Gland (Pheochromocytoma), Am. J. Cancer **29**:301-306 (Feb.) 1937. (*d*) Fischer, H.: Bestimmung des Adrenalingehaltes des Nebennierentumors, Ztschr. f. klin. Med. **134**:184-195 (May) 1938. (*e*) Kelly, H. M.; Piper, M. C.; Wilder, R. M., and Walters, W.: Case of Paroxysmal Hypertension with Paraganglioma of the Right Suprarenal Gland, Proc. Staff Meet., Mayo Clin. **11**:

in the blood stream of patients during a hypertensive crisis have been fraught with great difficulties. Beers, King and Prinzmetal,[94] in 1937, using blood taken from a patient during such an attack, were able to demonstrate abnormal quantities of a pressor substance in the blood by perfusing it through the denervated ear of a rabbit. Moreover, they presented convincing evidence that this substance probably was epinephrine.

The diagnosis is associated with great difficulty, especially if the patient is not under observation during an attack, or if the hypertension is relatively continuous, rather than paroxysmal. Various authors have suggested a number of methods for the production of a hypertensive crisis, although the hazards incident to such procedures are sufficiently obvious. In some cases palpation of the renal region not only has precipitated a crisis but has helped to localize the tumor to one side.[93g]

The treatment of such a tumor is surgical. Brunschwig and his associates [85] have emphasized the importance of prompt diagnosis and treatment because of the ever present menace of a fatal attack. Baumgarten and Cantor [95] reported a case in which death occurred from coronary occlusion. Cerebral and renal damage, as well as cardiac failure, in this patient could be attributed to repeated attacks of adrenal crises for nine years. Necropsy disclosed a small pheochromocytoma attached to the right kidney, several centimeters from the adrenal gland.

Successful removal of the tumor has been followed in almost every instance by cure. Surgical operation on these patients often has been extremely hazardous, death having occurred in a number of instances during the operation. MacKenzie and McEachern,[93f] in 1938, could find reports of only 15 cases in which attempted surgical removal of a pheochromocytoma had been successful. A number of cases in which operation was successful have been published since. A detailed description of a successful operative technic was described by MacKenzie and McEachern.[93f]

67-70 (Jan. 29) 1936. (*f*) MacKenzie, D. W., and McEachern, D.: Adrenal Pheochromocytoma, the Syndrome of Paroxysmal Hypertension: Report of a Case and Relief by Operation, Tr. Am. A. Genito-Urin. Surgeons **31**:127-154, 1938. (*g*) Strömbeck, J. P., and Hedberg, T. P.: Tumor of the Suprarenal Medulla Associated with Paroxysmal Hypertension, Acta chir. Scandinav. **82**: 177-189, 1939. (*h*) Estiu and Laborde.[35d] (*i*) Edward.[91b]

94. Beers, E.; King, F. H., and Prinzmetal, M.: Pheochromocytoma with Demonstration of a Pressor (Adrenalin) Substance in the Blood Preoperatively During Hypertensive Crisis, Ann. Surg. **106**:85-91 (July) 1937.

95. Baumgarten, E. C., and Cantor, M. O.: Pheochromocytoma: Case Report, Ann. Surg. **111**:112-116 (Jan.) 1940.

A number of instances have been reported in which bilateral chromaffin tumors of the adrenal medulla have been associated with cutaneous neurofibromatosis. Rosenthal and Willis [96] in 1936 collected 6 cases of this curious syndrome from the literature and added a seventh. The cases discussed by these authors were not associated with the syndrome of medullary hyperadrenalism, but von Brenner and his associates [93b] in 1938 reported the same association of symptoms in a patient who had paroxysmal hypertension. The tumor in this case was found to contain 1,200 mg. of epinephrine.

96. Rosenthal, D. B., and Willis, R. A.: The Association of Chromaffin Tumors with Neurofibromatosis, J. Path. & Bact. **42**:599-603 (May) 1936.

Correspondence

CHEMICAL FACTORS IN THE FORMATION OF GALLSTONES

To the Editor:—Some of the theories of gallstone formation are concerned with the maintenance of the solution of cholesterol in bile. About eleven years ago E. L. Walsh and A. C. Ivy (Observations on the Etiology of Gallstones, *Ann. Int. Med.* **4**:134 [Aug.] 1930) published results that seemed to indicate that the fatty acids or soaps in the bile exerted a more pronounced effect on cholesterol solubility than the bile acids. The former are in greater concentration in dog bile than in human bile, and this, according to Walsh and Ivy, accounts for the rarity of cholelithiasis in dogs and its frequency in human beings.

Later work by Dolkart, Jones and Brown from the same laboratory (Chemical Factors Concerned in the Formation of Gallstones, ARCH. INT. MED. **62**:618 [Oct.] 1938) supports this idea. The solubility of gallstone tablets was tested in a bile fraction that was obtained as follows: (Page 626 et seq.) An equal volume of alcohol was added to the bile and the filtrate was saponified with alkali. The nonsaponifiable insoluble fraction consisted of cholesterol to the extent of 80 per cent. The saponifiable or "fatty acid" fraction was used in the solubility experiments. As there was no mention made of separating the bile salts from the soaps, it appears that in every case this fraction contained both constituents. Yet these experiments led the authors to state that the solvent capacity of bile could be isolated in the fatty acid fraction. Later (page 630) they made the following statement: "In table 8 we attempted to correlate the relative activity of the various fatty acids as soaps on the basis of their molar concentration. . . . There was no correlation—indicating that the solvent activity was chiefly a chemical phenomenon." How this conclusion was obtained is not at all clear to us.

The average cholesterol content of human gallbladder bile is 0.3 per cent (Sobotka, H.: Physiological Chemistry of the Bile, Baltimore, Williams & Wilkins Company, 1937, p. 19), and according to Walsh and Ivy, dog gallbladder bile contains about one quarter of this amount. The ratio of soaps to cholesterol in dog bile is about twenty to one. While Dolkart, Jones and Brown maintained that sodium oleate in equal concentration dissolves four times more cholesterol than sodium cholate, it can be shown that the bile salts in dog bile are more than sufficient to dissolve the cholesterol contained therein. Let us assume that sodium taurocholate is present in dog bile in a concentration of 10 per cent. This is fair because sodium taurocholate is a relatively poor solvent for cholesterol (Bashour, J. T., and Bauman, L.: The Solubility of Cholesterol in Bile Salt Solutions, *J. Biol. Chem.* **121**:1, 1937), and 10 per cent is a conservative estimate for the concentration of bile acids in the gallbladder bile of dogs (Pickens, M.; Spanner, G. O., and Bauman, L.: The Composition of Gall Stones and Their Solubility in Dog Bile, *J. Biol. Chem.* **95**:505, 1932). Such a solution will dissolve almost twice the cholesterol that is present in the gallbladder of the dog.

Other statements contained in the article by Dolkart, Jones and Brown are equally open to question. For example, they spoke of the more frequent occurrence of gallstones in the human being, ox and hog than in the dog, cat, rabbit and sheep and intimated that the difference is due to a factor common to the group.

However, human gallstones consist almost entirely of cholesterol, ox gallstones of calcium bilirubinate and hog gallstones of lithocholate, that is, three substances with different chemical and physical properties. Should they not be considered individually rather than collectively?

The solubility values of pure cholesterol in pure bile salt solutions as determined by Bashour and Bauman are not in agreement with those of Dolkart, Jones and Brown. With compressed tablets of powdered gallstones Dolkart, Jones and Brown obtained an almost equal solubility in 5 per cent sodium cholate and sodium desoxycholate solution, whereas Bashour and Bauman obtained a 250 per cent greater solubility of pure cholesterol in the latter as compared with the former bile salt. This is in agreement with A. Rosin (Ueber die Lösung von Gallensteinen, *Ztschr. f. physiol. Chem.* **124**:282, 1923). Dolkart, Jones and Brown obtained the greatest cholesterol solubility in sodium cholate and progressively less in sodium taurocholate, sodium desoxycholate and sodium glycocholate. These results are also at variance with those of Bashour and Bauman. Our solubility values, using finely powdered, chemically pure substances, were reversibly tested and are to be considered as true solutions reproducible within the experimental error. At this point it may be well to emphasize that the immediate problem is the crystallization of cholesterol from bile and not the dissolution of concrements.

In a more recent article Dolkart, Lorenz, Jones and Brown (Relation of Fatty Acids and Bile Salts to the Formation of Gallstones, ARCH. INT. MED. **66**:1087 [Nov.] 1940) reported the study of the solubility of cholesterol tablets in solutions of the sodium salts of fatty and bile acids at a temperature of 70 C. The bearing of these data on conditions that obtain in the human gallbladder is not clear; it suggests that at body temperature the solvent effect of these salts is too slight to warrant a study of cholesterol solubility.

The solubility of cholesterol in 5 and 10 per cent soap solutions, which they reported, also has little bearing on conditions in the human gallbladder, since such concentrations, especially the higher, have rarely, if ever, been reported in human bile. The sudden drop in solvent capacity of bile when diluted by water can readily be explained by the known properties of bile salt solution, as indicated in the solubility studies of Bashour and Bauman.

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News and Comment

Salmon Memorial Lectures.—Dr. Robert D. Gillespie, psychiatric specialist of the British Royal Air Force, has been granted special leave of absence by the British government for the express purpose of delivering the Thomas William Salmon Memorial Lectures in the United States and Canada. These lectures, which have been titled "Psychoneuroses in Peace and War and the Future of Human Relationships," will be given, under the auspices of the Salmon Committee on Psychiatry and Mental Hygiene, in New York city on November 17 and 18, in Toronto, Canada, on November 19, in Chicago on November 21, in New Orleans on November 22, in Washington, D. C., on November 24 and 25, in San Francisco on November 27 and in Philadelphia on November 30. Dr. Gillespie will also make a report to members of the American medical profession and officers of the Morale Division of the United States Army and Navy in Hartford, Conn., on the psychologic effects of "Blitz" warfare on civilian and armed forces.

Book Reviews

Clinical Immunology, Biotherapy and Chemotherapy in the Diagnosis, Prevention and Treatment of Disease. By John A. Kolmer, M.D., Professor of Medicine, Temple University School of Medicine, and Louis Tuft, M.D., Assistant Professor of Medicine, Temple University School of Medicine. Price, $10. Pp. XIII + 941, with 27 illustrations, including 11 color plates. Philadelphia: W. B. Saunders Company, 1941.

This book is well printed on good paper and is clearly illustrated. It is a comprehensive volume of 36 chapters divided into two distinct parts. The first part takes up about a third of the entire book and deals with the general aspects of infection, immunity and chemotherapy. The second, and longer, part is clinical in nature and discusses the practical application of immunity and chemotherapy to the prevention and treatment of disease. This is a bare outline of the skeleton of the volume.

Each chapter is well and clearly written in a style that any student or practitioner will appreciate. The sentences are terse and to the point. The subdivisions of each chapter are clearly marked off, so that one can easily find just what one is looking for. Outlines of diagnostic surveys or summaries of diseases are incorporated in an ingenious tabular form which willy-nilly catches the reader's eye and demands notice. The color plates showing the result of vaccination, cutaneous tests or such procedures are satisfyingly graphic. Best of all, each chapter ends with a brief summary and a carefully selected bibliography germane to the matter under consideration.

On the whole, this book has all the earmarks of a successful medical text. Countless students and physicians will procure it, studying it and underlining their favorite parts with the same meticulous care that its authors displayed in writing it.

Objective and Experimental Psychiatry. By D. Ewen Cameron, M.D. Second edition. Price, $3.75. Pp. 390. New York: The MacMillan Company, 1941.

The author observes the unity of the organism with its environment and the necessity of studying the reactions of the whole organism, but expresses the belief that "habitually coordinated activities exist within the human organism which have as good a claim to be studied as wholes as does the whole represented by the organism itself." He scales the functions of the organism on the basis of the speed and extent to which they promote adaptation. At the top of the scale are learning and remembering. Lower level functions include autonomic and metabolic activities, and lowest in the scale are those functions which take many generations to develop. Tension, emotion and mood are well considered from the standpoint that "tension is a state of psychobiological preparedness." The latest work on sleep, convulsive disorders, metabolic activities, drugs, endocrine glands and heredity is all considered in its relation to upper level functions. A large amount of pertinent psychologic and physiologic research is critically examined. The book needs a summarizing chapter.

Lymphatics, Lymph and Lymphoid Tissue: Their Physiological and Clinical Significance. By Cecil Kent Drinker and Joseph Mendel Yoffey. Price, $4. Pp. 406, with 50 illustrations and 44 tables. Cambridge, Mass.: Harvard University Press, 1941.

This monograph deals with the physiologic and clinical significance of the lymphatic apparatus in mammals. It is a revision and extension of a previous monograph by Drinker and Field. The anatomic and physiologic organization

of the lymphatic system, the permeability of blood capillaries and its relation to lymph formation, the functional significance of lymphoid tissue and the composition and flow of lymph are dealt with extensively and authoritatively. The necessity of a knowledge of the physiology of the lymphatic system to an understanding of numerous clinical problems, such as edema, inflammation and surgical shock, is clearly pointed out. The clinician will find much of value and the biologic investigator a wealth of stimulating ideas in this clearly written and well documented treatise.

Diseases of the Nails. By V. Pardo-Castello, M.D., Assistant Professor of Dermatology and Syphilology, University of Habana. With a foreword by Howard Fox, M.D., Professor of Dermatology and Syphilology, New York University College of Medicine. Second Edition. Price, $3.50. Pp. XXI + 193, with 98 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1941.

This edition is practically a reprint of the first one, with 4 more illustrations, a few more pages and an up-to-date bibliography. The ARCHIVES (**60**:1114 [Dec.] 1937) and *The Journal of the American Medical Association* (**108**:232-233 [Jan. 16] 1937) each reviewed the original volume, favorably calling it, in effect, a useful monograph on an unusual subject, practical, short, plainly written and well illustrated. Those who do not own the first edition will be glad to know of the second. It continues to be an excellent small book to have on hand for reference.

Synopsis of Applied Pathological Chemistry. By Jerome E. Andes and A. G. Eaton. Price, $4. Pp. 428, with 23 illustrations and 35 tables. St. Louis: C. V. Mosby Company, 1941.

Ever since Vierordt published his famous "Tabellen" many years ago the need of compendiums of medical data has been recognized. No one can carry in his head all the values for physiologic, anatomic and chemical constants useful in clinical medicine; no one can keep in mind the details of the many biologic tests in current use. Synopses like this book, which in addition to technical details have some discussion of interpretation, are always useful, but their very briefness and hence dogmatic tendency may be criticized. The present volume contains a mine of useful material and could well have a place on the physician's shelf, or even in his bag.

Cardiac Clinics. By Fredrick A. Willius. Price, $4. Pp. 276, with 35 illustrations. St. Louis: C. V. Mosby Company, 1941.

These are the days of superspecialization, and almost every internist wants to be a cardiologist. Cardiology is a clearcut definite subject and one which involves attractive methods of precision, such as electrocardiography. As a result there has literally been a flood of monographs during the past four years on various aspects of heart disease. Dr. Willius uses the case history method to present vividly the outstanding features of cardiac disorders. A case or two each night should make good and useful bedtime reading for the tired practitioner. The volume is attractively got up and is full of excellent photographs and charts.

Handbook of Communicable Diseases. By Franklin H. Top and collaborators. Price, $7.50. Pp. 682, with 73 illustrations and 10 color plates. St. Louis: C. V. Mosby Company, 1941.

This excellent book calls to mind that there are few satisfactory treatises on communicable diseases in English. The authors' experience with purely clinical problems as well as with those concerning public health and isolation hospitals results in a happy combination for the student of the subject. The discussions

are well written and include recent advances in knowledge; the illustrations (many of them in color) are excellent, and the chapters on the technic of dealing with communicable disease are especially valuable.

Microbes Which Help to Destroy Us. By Paul W. Allen, D. Frank Holtman and Louise Allen McBee. Price, $3.50. Pp. 540, with 105 illustrations and 13 color plates. St. Louis: C. V. Mosby Company, 1941.

Here in semipopular style but with accuracy of fact are told the stories of the principal infectious diseases. The authors use the historical approach, and the biographic material about the great pioneers in bacteriology is pleasantly presented. This book makes ideal vacation reading for the medical student or physician, or even for the intelligent layman.

Hypertonie und Sklerose der Blutstrombahn. By Prof. Dr. Med. Fritz Lange. Price, 18 marks. Pp. 224. Leipzig: Theodor Steinkopff, 1941.

In this the fifth in a series of monographs on the circulation, the author discusses the clinical aspects, pathology, etiology, genesis and treatment of hypertension and vascular sclerosis.

Although the book makes interesting reading, the reviewer can hardly recommend it to any one desiring a thorough and detailed insight into this subject.

CORRECTION

In the article by Oliver P. Jones, Ph.D., entitled "Transmission of Antianemic Principle Across the Placenta and Its Influence on Embryonic Erythropoiesis: I. Quantitative Effect of Diets Containing Ventriculin" (Arch. Int. Med. **68**:476 [Sept.] 1941), the last three lines in the paragraph preceding "Observations" on page 484 should have been incorporated in reference 47, at the bottom of the page.